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L2           185 S E3,E5-E9
L3            22 S E118
                E DEHAVEN/AU
L4            16 S E9-E11
L5            48 S E15-E18
                E HUDKINS/AU
L6             1 S E4
                E GAUL F/AU
L7            16 S E3-E5
                E KUMAR V/AU
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                E KUMAR VIRENDRA/AU
L9            95 S E3
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L11            1 S E5 .
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L12           24 S E3,E5,E6
                E MAYCOCK A/AU
L13           64 S E3,E4,E6,E8,E9
                E ZHANG W/AU
L14          554 S E3,E22
                E ZHANG WEI/AU
L15         1248 S E3,E69
                E ZHANG WEIYUAN/AU
L16           23 S E3
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L18          889 S E5,E6
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                E ITCH/CW
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L20          890 S E5,E4+NT
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L22         1629 S E5-E21
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L23           74 S E4-E8
                E ITCH
L24         1292 S E3,E6,E9,E10,E15,E16,E17,E22
                E SCRATCH
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L26            8 S E24,E26,E34
L27           29 S E38
L28            1 S E37
                E ANTIITCH
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                E ANTIPRUR
L30          274 S E5-E12
L31            2 S E93
L32            1 S E103
                E ANTISCRATCH
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L33          129 S E3,E4,E5
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L34          110 S E4-E6
L35        20532 S L18-L34
L36         2743 S KAPPA(L)RECEPTOR(L)AGONIST(L)(OPIOID? OR OPIAT?)
L37         4877 S KAPPA(L)RECEPTOR(L)(OPIOID? OR OPIAT?)
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L39           46 S L35 AND L37
L40          115 S (OPIOID? OR OPIAT?)(L)AGONIST AND L35
L41          235 S (OPIOID? OR OPIAT?)(L)RECEPTOR AND L35
L42           57 S (OPIOID? OR OPIAT?)(L)KAPPA AND L35
L43           57 S L38,L39,L42
L44          200 S L40,L41 NOT L43
L45           41 S KAPPA(L)AGONIST AND L35
L46           58 S L43,L45
L47          200 S L40,L41 NOT L46
L48            5 S L17 AND L46
L49            1 S L17 AND L47
L50            6 S L48,L49
                 E ADOLOR/PA,CS
L51           30 S E3-E14
L52           14 S L51 AND L35
L53            9 S L51 AND L36,L37
L54           17 S L51 AND  (OPIOID? OR OPIAT?)(L)(AGONIST OR  RECEPTOR OR KAPPA
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L56            7 S L53,L54 AND L52
L57            7 S L50,L56
L58           17 S L52-L55 NOT L57
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L63           16 S L60 AND PRURITUS/CW,BI
L64           50 S L62,L63

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=> d l64 bib abs tot

L64 ANSWER 1 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2002:2292 HCAPLUS
TI Alvimopan* (ADL 8-2698) Is a Novel Peripheral Opioid Antagonist
AU Schmidt, William K.
CS **Adolor Corporation, Exton, PA, 19341-1127, USA**
SO American Journal of Surgery (2001), 182(5A), 27S-38S
CODEN: AJSUAB; ISSN: 0002-9610
PB Excerpta Medica, Inc.
DT Journal
LA English
AB Alvimopan (ADL 8-2698; Adolor Corporation, Exton, PA, USA) is a novel, peripherally restricted **opioid** antagonist. After oral administration, it has activity specific to the gastrointestinal (GI) tract. ADL 8-2698 has low systemic absorption and a high affinity for .mu.-**opioid receptors**. In healthy subjects, ADL 8-2698 antagonized loperamide-induced changes in GI transit and prevented morphine-induced delays in oral-cecal transit time without antagonizing centrally mediated **opioid** effects, such as analgesia or pupillary constriction. In the treatment of **opioid** naive patients who underwent surgery and received **opioids** for acute pain, oral ADL 8-2698 (6.0 mg) improved the management of postoperative ileus (POI) by shortening the time to achieve normal bowel function and, ultimately, hospital stay. Postoperative nausea and vomiting and the overall incidence of all GI side effects were reduced in patients treated with ADL 8-2698 for POI. Analgesia was not compromised, because there were no changes in median **opioid** consumption or Visual Analog Scale (VAS) pain scores in patients treated with ADL 8-2698 vs. patients treated with placebo. No drug-related side effects were obsd. in acute pain postsurgical patients in the initial POI study. In patients treated with **opioids** for chronic pain or **opioid** addiction, lower doses of oral ADL 8-2698 (0.5 to 3.0 mg) reversed **opioid** bowel dysfunction (OBD) and normalized GI activity. These effects were evident without compromising **opioid** analgesia or inducing central nervous system symptoms of withdrawal. Some chronic **opioid** patients receiving apparently supramaximal doses of ADL 8-2698 (.gtoreq.3.0 mg) reported localized GI side effects, possibly indicative of a localized GI withdrawal response. The most common side effects of ADL 8-2698 in chronic pain patients with OBD were abdominal pain, flatulence, and diarrhea. These effects were not obsd. in most OBD patients receiving lower doses of ADL 8-2698. Overall, ADL 8-2698 was well tolerated in clin. trials. Further studies to evaluate the efficacy and safety of ADL 8-2698 in clin. practice are in progress.

L64 ANSWER 2 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:833071 HCAPLUS
DN 135:352822
TI **Opioid agonist** and antagonist compositions and methods for enhancing potency or reducing adverse side effects of **opioid agonists**
IN Sherman, Barry; Remien, Mary; Barbier, Remi; Dumas, Kathleen; Schoenhard, Grant
PA Pain Therapeutics, Inc., USA; Albert Einstein College of Medicine of Yeshiva University
SO PCT Int. Appl., 835 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001085150	A2	20011115	WO 2001-US14644	20010504
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LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6011004	A	20000104	US 1996-768221	19961217	<--
AU 9947399	A1	19991028	AU 1999-47399	19990906	<--
WO 2000067739	A2	20001116	WO 2000-US12493	20000505	
WO 2000067739	A3	20010125			

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PRAI US 2000-202227	P	20000505		
US 2000-202268	P	20000505		
US 2000-566071	A	20000505		
WO 2000-US12493	W	20000505		
US 2000-244482	P	20001030		
US 2000-245110	P	20001101		
US 2000-246235	P	20001102		
US 2001-756331	A	20010108		
US 1990-612847	B1	19901113	<--	
US 1993-153796	A1	19931117	<--	
AU 1995-32769	A3	19950718	<--	
US 1999-306164	A2	19990506		

AB The invention provides compns. and methods using an **opioid agonist** and an **opioid** antagonist to differentially dose a human subject so as to either enhance analgesic potency without attenuating an adverse side effect of the **agonist**, or alternatively maintain the analgesic potency of the **agonist** while attenuating an adverse side effect of the **agonist**. The invention addnl. relates to novel **opioid** compns. and methods for the gender-based dosing of men and women.

L64 ANSWER 3 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:757813 HCAPLUS
DN 135:318517
TI Preparation of 1-aralkanoyl-2-pyrrolidinomethylpiperazines and analogs as **.kappa.-opioid receptor agonists**
IN Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael Anthony; Kumar, Virendra; Gaul, Forrest; Chang, An-Chih; Guo, Deqi
PA **Adolor Corporation, USA**
SO U.S., 115 pp., Cont.-in-part of U.S. 5,945,443.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 7

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6303611	B1	20011016	US 1998-150369	19980909
US 5646151	A	19970708	US 1996-612680	19960308
US 5688955	A	19971118	US 1997-796078	19970205
US 5744458	A	19980428	US 1997-899086	19970723
US 5945443	A	19990831	US 1998-34661	19980303
US 6057323	A	20000502	US 1998-183011	19981030
US 6054445	A	20000425	US 1999-307387	19990507
WO 2000014065	A1	20000316	WO 1999-US13680	19990616

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD,

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO,
RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE

	AU 9944428	A1	20000327	AU 1999-44428	19990616
	EP 1112252	A1	20010704	EP 1999-927550	19990616
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 6239154	B1	20010529	US 1999-372191	19990811
PRAI	US 1996-612680	A1	19960308		
	US 1997-796078	A3	19970205		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
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	US 1998-183011	A3	19981030		
	WO 1999-US13680	W	19990616		

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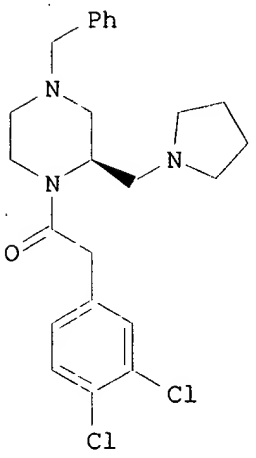

I

AB Title compds., e.g., I, were prepd. Data for biol. activity of title compds. were given.

RE.CNT 17

RE

(1) Anon; EP 0147085 1984 HCAPLUS
(3) Anon; EP 0233793 1987 HCAPLUS
(4) Anon; EP 0330461 1989 HCAPLUS
(5) Anon; EP 0330467 1989 HCAPLUS
(6) Anon; EP 0366327 1989 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 4 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:434812 HCAPLUS
DN 135:29160
TI Methods using peripheral .mu. opioid antagonists for the treatment and prevention of dizziness and **pruritus**
IN Carpenter, Randall L.
PA **Adolor Corporation, USA**
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001041705	A2	20010614	WO 2000-US42310	20001129
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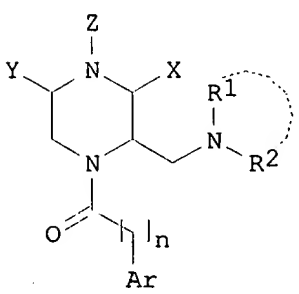
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001041369 A5 20010618 AU 2001-41369 20001129
PRAI US 1999-450812 A 19991129
WO 2000-US42310 W 20001129
OS MARPAT 135:29160
AB Methods are provided for the treatment and/or prevention of dizziness and/or **pruritus**. The methods may comprise administering to a patient an effective amt. of a peripheral .mu. opioid antagonist compd. Preferred compds. for use in the methods include piperidine-N-alkylcarboxylates, quaternary morphinans, opium alkaloid derivs. and quaternary benzomorphans. The methods are particularly suitable for treating and/or preventing dizziness and/or **pruritus** assocd. with opioid compds.

L64 ANSWER 5 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:392068 HCAPLUS
DN 135:5628
TI Preparation of 1-acyl-2-pyrrolidinylmethylpiperazines and related compounds as **.kappa. agonists**.
IN **Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael Anthony; Kumar, Virendra; Gaul, Forrest;** Guo, Deqi
PA **Adolor Corporation, USA**
SO U.S., 119 pp., Cont.-in-part of U.S. Ser. No. 150,369.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6239154	B1	20010529	US 1999-372191	19990811
	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 6303611	B1	20011016	US 1998-150369	19980909
PRAI	US 1996-612680	A2	19960308		
	US 1997-796078	A3	19970205		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
	US 1998-150369	A2	19980909		

OS MARPAT 135:5628
GI



I

AB Title compds., e.g., [I; n = 1-3; R1, R2 = Me, (CH2)m, CH2CH(OH)(CH2)2;

CH2CHF(CH2)2, etc.; m = 4-8; Ar = (substituted) Ph, benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl, 9-fluorenyl; Z = PO3H2, (CH2)pCO2H, SO2Me, SO2NH2, tetrazolylmethyl, etc.; p = 0-20; X, Y = CH2NHSO2Me, CH2NHPO3H2, (CH2)qO(CH2)qSO3H, etc.; q = 1-20], were prepd. Thus, Me (R,S)-4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate hydrochloride (prepn. outlined) at 300 mg gave 98% inhibition of formalin-induced nociception in rat paws.

RE.CNT 2
RE
(1) Kruse; US 5688955 1997 HCAPLUS
(2) Kruse; US 5945443 1999 HCAPLUS

L64 ANSWER 6 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:844938 HCAPLUS
DN 134:115816
TI Arylacetamides as peripherally restricted **kappa opioid receptor agonists**
AU Kumar, Virendra; Marella, Michael A.; Cortes-Burgos, Luz; Chang, An-Chih; Cassel, Joel A.; Daubert, Jeffrey D.; DeHaven, Robert N.; DeHaven-Hudkins, Diane L.; Gottshall, Susan L.; Mansson, Erik; Maycock, Alan L.
CS **Adolor Corporation, Malvern, PA, 19355, USA**
SO Bioorg. Med. Chem. Lett. (2000), 10(22), 2567-2570
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB Analogs of the **.kappa.-opioid receptor agonist**, ICI 199441, were prepd. Ki values for these analogs at the cloned human **.kappa. opioid receptor** ranged from 0.058 to 25 nM. Trifluoromethylaryl derivs. were potent analgesics when administered s.c. in the rat and were more peripherally restricted than the parent compd., ICI 199441.

RE.CNT 12
RE
(1) Barber, A; Exp Opin Invest Drugs 1997, V6, P1351 HCAPLUS
(2) Barlow, J; J Med Chem 1991, V34, P3149 HCAPLUS
(3) Chang, A; J Med Chem 1994, V37, P4490 HCAPLUS
(4) Costello, G; Eur J Pharm 1988, V151, P475 HCAPLUS
(5) Costello, G; J Med Chem 1991, V34, P181 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 7 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:814295 HCAPLUS
DN 133:329619
TI Compositions and methods using an opioid antagonist for enhancing analgesic potency of tramadol and attenuating its adverse side effects
IN Crain, Stanley M.; Shen, Ke-Fei; Sherman, Barry; Remien, Mary; Barbier, Remi; Friedmann, Nadav
PA Pain Therapeutics, Inc., USA; Albert Einstein College of Medicine of Yeshiva University
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000067739	A2	20001116	WO 2000-US12493	20000505
	WO 2000067739	A3	20010125		

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US 6011004 A 20000104 US 1996-768221 19961217 <--
US 2001006967 A1 20010705 US 1999-306164 19990506 <--
AU 9947399 A1 19991028 AU 1999-47399 19990906 <--
WO 2001085257 A2 20011115 WO 2001-US14377 20010504
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WO 2001085150 A2 20011115 WO 2001-US14644 20010504
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US 1990-612847 B1 19901113 <--
US 1992-947690 B2 19920921 <--
US 1993-97460 A2 19930727 <--
US 1993-153796 A1 19931117 <--
US 1994-276966 A2 19940719 <--
AU 1995-32769 A3 19950718 <--
US 1996-759590 A1 19961203 <--
US 1998-94977 A2 19980616
US 2000-202227 P 20000505
US 2000-202268 P 20000505
US 2000-566071 A 20000505
WO 2000-US12493 W 20000505
US 2000-244482 P 20001030
US 2000-245110 P 20001101
US 2000-246235 P 20001102
US 2001-756331 A 20010108

AB The invention provides compns. and methods with tramadol and an **opioid** antagonist to enhance analgesic potency and/or attenuate one or more adverse effects of tramadol, including adverse side effect(s) in humans such as nausea, vomiting, dizziness, headache, sedation (somnolence) or **pruritis**. Compns. and methods are provided for selectively enhancing the analgesic potency of tramadol and simultaneously attenuating anti-analgesia, hyperalgesia, hyperexcitability, phys. dependence and/or tolerance effects assocd. with the administration of tramadol. The methods of the invention comprise administering to a subject an analgesic or subanalgesic amt. of tramadol and an amt. of excitatory **opioid receptor** antagonist, e.g. naltrexone or nalmefene, effective to enhance the analgesic potency of tramadol and attenuate the anti-analgesia, hyperalgesia, hyperexcitability, phys. dependence and/or tolerance effects of tramadol.

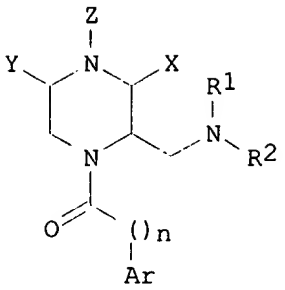
L64 ANSWER 8 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:331874 HCAPLUS
TI Synthesis and evaluation of novel peripheral .**kappa**. **opioid receptor agonists**.
AU Guo, Deqi; Kumar, Virendra; Maycock, Alan; DeHaven, Robert N.; Daubert, Jeff D.; Cassel, Joel A.; Gauntner, Erin K.; DeHaven-Hudkins, Diane L.; Gottshall, Susan L.; Greiner, Susan; Koblish, Mike; Little, Pat J.
CS **Adolor Corporation, Malvern, PA, 19355, USA**
SO Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March

26-30, 2000 (2000), MEDI-263 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69CLAC
DT Conference; Meeting Abstract
LA English
AB Although centrally active .**kappa**. **agonists** have analgesic properties, they have been of limited therapeutic use because of side effects such as sedation, dysphoria and diuresis. Recent evidence indicates that the **opioid** antinociception can also be mediated by activation of **opioid receptors** located outside the CNS. One of the goals at Adolor is to modify centrally active .**kappa**. **agonists** to reduce CNS penetration, thus eliminating or minimizing the side effects. We have recently reported 2-(4-trifluoromethylphenyl)-N-methyl-N-[1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide 1 as a highly potent .**kappa**. **agonist** with a profile of peripheral selectivity better than that of centrally active ICI 199441 (2). To improve the peripheral selectivity of 1, we have synthesized a series of analogs of general structure 3 modified in the central Ph ring and evaluated them for in vitro binding affinity, in vivo antinociceptive activity, and peripheral selectivity. The synthetic strategy and the results from the biol. studies will be presented.

L64 ANSWER 9 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:284003 HCAPLUS
DN 132:293778
TI Preparation of 1-acyl-2-pyrrolidinylmethylpiperazines and related compounds as .**kappa**. **agonists**.
IN **Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael Anthony; Kumar, Virendra; Gaul, Forrest; Chang, An-chih;** Guo, Deqi
PA **Adolor Corporation, USA**
SO U.S., 121 pp., Cont.-in-part of U.S. Ser. No. 150,369.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6057323	A	20000502	US 1998-183011	19981030
	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 6303611	B1	20011016	US 1998-150369	19980909
	US 6054445	A	20000425	US 1999-307387	19990507
PRAI	US 1996-612680	A1	19960308		
	US 1997-796078	A3	19970205		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
	US 1998-150369	A2	19980909		
	US 1998-183011	A3	19981030		

OS MARPAT 132:293778
GI



I

AB Title compds., e.g., [I; n = 1-3; R1, R2 = Me, (CH2)m, CH2CH(OH)(CH2)2; CH2CHF(CH2)2, etc.; m = 4-8; Ar = (substituted) Ph, benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl, 9-fluorenyl; Z = PO3H2, (CH2)pCO2H, SO2Me, SO2NH2, tetrazolylmethyl, etc.; p = 0-20; X, Y = CH2NHSO2Me, CH2NHPO3H2, (CH2)qO(CH2)qSO3H, etc.; q = 1-20], were prepd. as analgesics and anti-**pruritic** agents. Thus, Me (R,S)-4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate hydrochloride (prepn. outlined) at 300 mg gave 98% inhibition of formalin-induced nociception in rat paws.

RE.CNT 26

RE

(1) Anon; EP 0147085 1984 HCAPLUS
(2) Anon; EP 0207773 1986 HCAPLUS
(3) Anon; EP 0233793 1987 HCAPLUS
(4) Anon; EP 0330461 1989 HCAPLUS
(5) Anon; EP 0330467 1989 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 10 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:260010 HCAPLUS
DN 132:298831
TI Peripherally acting anti-**pruritic** opiates
IN Farrar, John J.; Cowan, Alan
PA **Adolor Corporation, USA**
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000021530	A1	20000420	WO 1999-US17439	19990802
	W: AL, AU, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KR, LC, LK, LR, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9952500	A1	20000501	AU 1999-52500	19990802
	EP 1119354	A1	20010801	EP 1999-937727	19990802
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LV, FI, RO				
	BR 9914380	A	20010807	BR 1999-14380	19990802
PRAI	US 1998-168724	A	19981009		
	WO 1999-US17439	W	19990802		

OS MARPAT 132:298831

AB Anti-**pruritic** compns. for the prevention or treatment of **pruritus** comprise e.g., morpholines, piperidines, oxadiazoles, phenylamidinoureas, and 1-azabicyclo[2.2.2]octanes. Thus, rectal suppositories contained loperamide 80, propylene glycol 95, and PEG-4000 1800 g. Loperamide at 2.5 mg/kg antagonized Compd. 48/80-induced **scratching** in a dose-dependent manner, as demonstrated in mice.

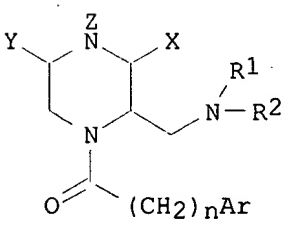
RE.CNT 3

RE
(1) Diamond; US 4203920 A 1980 HCAPLUS
(2) Park; US 5242944 A 1993 HCAPLUS
(3) Wals; US 4824853 A 1989 HCAPLUS

L64 ANSWER 11 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:175792 HCAPLUS
DN 132:222550
TI Preparation of 1-acyl-2-pyrrolidinylmethylpiperazines and related compounds as .**kappa**. **agonists**.
IN Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael Anthony; Kumar, Virendra; Gaul, Forrest; Chang, An-chih; Guo, Deqi
PA **Adolor Corp.**, **USA**
SO PCT Int. Appl., 216 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000014065	A1	20000316	WO 1999-US13680	19990616
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6303611	B1	20011016	US 1998-150369	19980909
	AU 9944428	A1	20000327	AU 1999-44428	19990616
	EP 1112252	A1	20010704	EP 1999-927550	19990616
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1998-150369	A	19980909		
	US 1996-612680	A1	19960308		
	US 1997-796078	A3	19970205		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
	WO 1999-US13680	W	19990616		

OS MARPAT 132:222550
GI



I

AB Title compds., e.g., [I; n = 1-3; R1, R2 = Me, (CH2)m, CH2CH(OH)(CH2)2; CH2CHF(CH2)2, etc.; m = 4-8; Ar = (substituted) Ph, benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl, 9-fluorenyl; Z = PO3H2, (CH2)pCO2H, SO2Me, SO2NH2, tetrazolylmethyl, etc.; p = 0-20; X, Y = CH2NHSO2Me, CH2NHPO3H2, (CH2)qO(CH2)qSO3H, etc.; q = 1-20], were prepd. Thus, Me (R,S)-4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate hydrochloride (prepn. outlined) at 300 mg gave 98% inhibition of formalin-induced nociception in rat paws.
RE.CNT 1
RE
(1) Lednicer; US 4065573 A 1977 HCAPLUS

L64 ANSWER 12 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1999:617474 HCAPLUS
TI Synthesis and chiral separation of the four diastereomers of GR 94839.
AU Gaul, Forrest E.; Zhang, Wei-Yuan; Maycock, Alan L.; DeHaven, Robert N.; Daubert, Jeffrey D.; Cassel, Joel A.; Mansson, Eric; Geiser, Fiona; Lee, James; Champion, William L., Jr.
CS Medicinal Chemistry, **Adolor** Corporation, Malvern, PA, 19355, USA
SO Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26 (1999), MEDI-102 Publisher: American Chemical Society, Washington, D. C. CODEN: 67ZJA5
DT Conference; Meeting Abstract
LA English
AB There is evidence that **kappa** (k) **agonists** with limited access to the central nervous system could be antinociceptive while lacking the side effects, such as sedation and dysphoria, produced by centrally active k **agonists**. GR 94839 (a mixt. of diastereomers), a k **opioid agonist** with limited access to the central nervous system, has been reported to be a potent analgesic in animals. As part of our peripheral **kappa** program, we have used GR 94839 as a template for structure modifications to improve k **receptor** binding and peripheral selectivity. One goal was to compare the **opioid receptor** binding activity of the four diastereomers of GR 94839 (). In our hands the reported chiral routes to these diastereomers yielded £ 40 %. The two racemic routes followed by chiral sepn. using a preparative CHIRALPAK AD column yielded all four diastereomers in high. The binding affinities of the diastereomers to m, d, and k **opioid receptors** will be presented.

L64 ANSWER 13 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:226280 HCAPLUS
DN 131:39586
TI Loperamide (ADL 2-1294), an opioid **antihyperalgesic** agent with peripheral selectivity
AU **DeHaven-Hudkins, D. L.**; Burgos, L. Cortes; Cassel, J. A.; Daubert, J. D.; DeHaven, R. N.; Mansson, E.; Nagasaka, H.; Yu, G.; Yaksh, T.
CS **Adolor Corporation, Malvern, PA, USA**
SO J. Pharmacol. Exp. Ther. (1999), 289(1), 494-502 CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB The **antihyperalgesic** properties of the **opiate** antidiarrheal agent loperamide (ADL 2-1294) were investigated in a variety of inflammatory pain models in rodents. Loperamide exhibited potent affinity and selectivity for the cloned .mu. (Ki = 3 nM) compared with the .delta. (Ki = 48 nM) and .**kappa**. (Ki = 1156 nM) human **opioid receptors**. Loperamide potently stimulated [35S]guanosine-5'-O-(3-thio)-phosphate binding (EC50 = 56 nM), and inhibited forskolin-stimulated cAMP accumulation (IC50 = 25 nM) in Chinese hamster ovary cells transfected with the human .mu. **opioid receptor**. The injection of 0.3 mg of loperamide into the intra-articular space of the inflamed rat knee joint resulted in potent antinociception to knee compression that was antagonized by naloxone, whereas injection into the contralateral knee joint or via the i.m. route failed to inhibit compression-induced changes in blood pressure. Loperamide potently inhibited late-phase formalin-induced flinching after intrapaw injection (A50 = 6 .mu.g) but was ineffective against early-phase flinching or after injection into the paw contralateral to the formalin-treated paw. Local injection of loperamide also produced antinociception against Freund's adjuvant- (ED50 = 21 .mu.g) or tape stripping- (ED50 = 71 .mu.g) induced hyperalgesia as demonstrated by increased paw pressure thresholds in the inflamed paw. In all animal models examd., the potency of loperamide after local administration was comparable to or better than that of morphine. Loperamide has potential therapeutic use as a peripherally selective **opiate**

antihyperalgesic agent that lacks many of the side effects generally assocd. with administration of centrally acting **opiates**

RE.CNT 41
RE
(1) Antonijevic, I; J Neurosci 1995, V15, P165 HCAPLUS
(2) Bare, L; FEBS Lett 1994, V354, P213 HCAPLUS
(3) Bianchi, C; Arzneim-Forsch/Drug Res 1977, V27, P1040 HCAPLUS
(4) Blake, A; J Biol Chem 1997, V272, P782 HCAPLUS
(5) Cabot, P; J Clin Invest 1997, V100, P142 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 14 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:212693 HCAPLUS
DN 130:257341
TI Film-forming compositions of **antihyperalgesic** opiates and method of treating hyperalgesic and **pruritic** conditions therewith
IN Farrar, John J.; Maycock, Alan L.; Kumar, Virendra; Balogh, Imre Jim
PA **Adolor Corporation, USA**
SO U.S., 13 pp., Cont.-in-part of U.S. 5,667,773.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5888494	A	19990330	US 1997-891924	19970714
	US 5667773	A	19970916	US 1996-614027	19960312
	WO 9903455	A1	19990128	WO 1998-US12834	19980619
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9880749	A1	19990210	AU 1998-80749	19980619
	AU 728538	B2	20010111		
	EP 1003489	A1	20000531	EP 1998-929109	19980619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001510152	T2	20010731	JP 2000-502756	19980619
	NO 9906351	A	20000310	NO 1999-6351	19991220
PRAI	US 1996-614027	A2	19960312		
	US 1997-891924	A	19970714		
	WO 1998-US12834	W	19980619		

AB Disclosed are topical film-forming compns. for the prevention and treatment of **pruritus** contg. (1) an opiate that is substantially devoid of central nervous system effects, (2) a film-forming polymeric material, and (3) an aq. pharmaceutically acceptable carrier. An emulsion contained loperamide.cntdot.HCl 30, ethanol 20, Na Et cellulose sulfate 25, Ca lactate 10, and water q.s. to 100 %.
RE.CNT 28
RE
(2) Anon; GB 933668 1963 HCAPLUS
(3) Anon; DE 2636559 1977 HCAPLUS
(7) Bernstein; Journal of Investigative Dermatology 1982, V78, P82 HCAPLUS
(8) Calvet; US 5236947 1993 HCAPLUS
(9) Clemente; US 5576346 1996 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 15 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:77462 HCAPLUS
DN 130:158399
TI Film-forming compositions of **antihyperalgesic** opiates and method of treating hyperalgesic and **pruritic** conditions therewith

IN Farrar, John J.; Maycock, Alan L.; Kumar, Virendra; Balogh, Imre
PA **Adolor Corporation, USA**
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9903455	A1	19990128	WO 1998-US12834	19980619
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5888494	A	19990330	US 1997-891924	19970714
AU 9880749	A1	19990210	AU 1998-80749	19980619
AU 728538	B2	20010111		
EP 1003489	A1	20000531	EP 1998-929109	19980619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001510152	T2	20010731	JP 2000-502756	19980619
NO 9906351	A	20000310	NO 1999-6351	19991220
PRAI US 1997-891924	A	19970714		
US 1996-614027	A2	19960312		
WO 1998-US12834	W	19980619		

AB Disclosed are topical film-forming compns. for the prevention and treatment of **pruritus** contg. an opiate that is substantially devoid of central nervous system effects. A topical prepn. contained loperamide.cntdot.HCl 25, Na carrageenan 25, Ca lactate 32, and water to 100 %.
RE.CNT 3
RE
(1) Blank, I; 26 36559DT A1 1977
(2) Clemente; US 5576346 A 1996 HCAPLUS
(3) Tunc; US 4623539 A 1986 HCAPLUS

L64 ANSWER 16 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:816107 HCAPLUS
DN 130:47476
TI Peripherally acting anti-**pruritic** opiates
IN Farrar, John J.; Cowan, Alan
PA **Adolor Corporation, USA**
SO U.S., 15 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5849762	A	19981215	US 1997-892194	19970714
WO 9903472	A1	19990128	WO 1998-US12831	19980619
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9878395	A1	19990210	AU 1998-78395	19980619
AU 725444	B2	20001012		
EP 1019051	A1	20000719	EP 1998-926595	19980619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

	BR 9810710	A	20000808	BR 1998-10710	19980619
	JP 2001510157	T2	20010731	JP 2000-502771	19980619
	ZA 9806207	A	19990126	ZA 1998-6207	19980713
	NO 9906354	A	20000308	NO 1999-6354	19991220
PRAI	US 1997-892194	A	19970714		
	WO 1998-US12831	W	19980619		

OS MARPAT 130:47476

AB Anti-**pruritic** compns. and methods of using the compns. for the prevention or treatment of **pruritus** comprising opiates in a pharmaceutically acceptable carrier. The mean anti-**pruritic** activity of 1-[3,3-diphenyl-3-(2-pyridyl)propyl]-4-phenyl-4-piperidinecarboyxlic acid hydrochloride at 10.0 mg/kg s.c. in rats was 83%. Formulation of different pharmaceutical dosage forms are also disclosed.

RE.CNT 34

RE

(1) Adelstein; US 4066654 1978 HCAPLUS
(2) Adelstein; US 4069223 1978 HCAPLUS
(3) Adelstein; US 4072686 1978 HCAPLUS
(5) Adelstein; US 4116963 1978 HCAPLUS
(6) Adelstein; US 4194045 1980 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 17 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:613444 HCAPLUS

DN 129:265466

TI Spray formulations of **antihyperalgesic** opiates and method of treating topical hyperalgesic conditions therewith

IN Maycock, Alan L.; Chang, An-chih; Farrar, John J.; Balogh, Imre

PA **Adolor Corp., USA**

SO U.S., 8 pp.
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5811078	A	19980922	US 1997-818559	19970314
	US 5798093	A	19980825	US 1997-892389	19970714
PRAI	US 1997-818559	A2	19970314		

OS MARPAT 129:265466

AB Spray formulations of anti-hyperalgesic opiates comprise an anti-hyperalgesic opiate having a peripheral selectivity of 251 to 1,280 in an aq. alc. mixt. contg. up to 15% ethanol, propanol, and/or isopropanol. Thus, 100 g of 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-.alpha.,.alpha.-diphenyl-1-piperidinebutyramide was dissolved in 2 L of a 5 % ethanol/95 % water mixt. with agitation and the soln. was transferred to a pump action spray bottle.

L64 ANSWER 18 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:572232 HCAPLUS

DN 129:221192

TI Spray formulations of **antihyperalgesic** opiates for treatment of **pruritus**

IN Farrar, John J.; Chang, An-chih; Maycock, Alan L.; Balogh, Imre

PA **Adolor Corp., USA**

SO U.S., 9 pp. Cont.-in-part of U.S. Ser. No. 818,559.
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5798093	A	19980825	US 1997-892389	19970714
	US 5811078	A	19980922	US 1997-818559	19970314
	WO 9903457	A1	19990128	WO 1998-US12832	19980619

W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU	9880748	A1	19990210	AU 1998-80748	19980619
AU	724727	B2	20000928		
EP	1011647	A1	20000628	EP 1998-929108	19980619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR	9810711	A	20000808	BR 1998-10711	19980619
JP	2001510153	T2	20010731	JP 2000-502758	19980619
NO	9906234	A	20000310	NO 1999-6234	19991216
PRAI US	1997-818559	A2	19970314		
US	1997-892389	A	19970714		
WO	1998-US12832	W	19980619		

OS MARPAT 129:221192

AB Spray formulations of anti-**pruritic** opiates having a peripheral selectivity of 251 to 1280 in a solvent mixt. of up to 15% alc. selected from the group consisting of EtOH, PrOH and iso-PrOH and water .gtoreq.85%. Thus, loperamide was prepd. by the reaction of 4-(p-chlorophenyl)-4-piperidinol with dimethyl(tetrahydro-3,3-diphenyl-2-furylidene)ammonium bromide in the presence of Na2CO3 and KI in 4-methyl-2-pentanone soln. Thus, 100 loperamide was dissolved in 2 L of EtOH-water (5:95) to form a spray.

L64 ANSWER 19 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:529782 HCAPLUS
TI Modified piperazine derivatives as peripherally selective **kappa opioid** analgesics
AU Zhang, Y.; Cassel, J.; Cortes-Burgos, L.; Daubert, J.; DeHaven, R.; DeHaven-Hudkins, D.; Gaul, F.; Gottshall, S.; Greiner, S.; Koblish, M.; Maycock, A.; Little, P.
CS **Adolor Corporation, Malvern, PA, 19355, USA**
SO Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), MEDI-297 Publisher: American Chemical Society, Washington, D. C. CODEN: 66KYA2
DT Conference; Meeting Abstract
LA English
AB There has been great interest by the pharmaceutical industry in the development of peripherally selective novel analgesics which act by activation of **.kappa.-opioid receptors**. . **kappa. agonists** posses advantage over .mu. **agonists** being devoid of side effects such as respiratory depression, constipation and phys. dependence. Modification on the known centrally active **.kappa. agonist** (1, GR 89696) gave a series of new compds. (2) with improved peripheral selectivity. The synthesis, SAR and in vivo data will be presented.

L64 ANSWER 20 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:397785 HCAPLUS
DN 129:67799
TI Preparation of 1,4-diacyl-2-(pyrrolidinomethyl)piperazines and analogs as **kappa opioid receptor agonists**
IN **Kruse, Lawrence I.; Chang, An-Chih; DeHaven-Hudkins, Diane L.**; Farrar, John J.; **Gaul, Forrest ; Kumar, Virendra; Marella, Michael Anthony; Maycock, Alan L.; Zhang, Wei Yuan**
PA **Adolor Corp., USA**
SO U.S., 67 pp., Cont.-in-part of U. S. 5,688,955. CODEN: USXXAM
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5763445	A	19980609	US 1997-891833	19970714
	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	US 5981513	A	19991109	US 1998-45522	19980321
	WO 9903468	A1	19990128	WO 1998-US12769	19980619
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9879801	A1	19990210	AU 1998-79801	19980619
	AU 725232	B2	20001012		
	EP 998281	A1	20000510	EP 1998-930400	19980619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9810712	A	20000905	BR 1998-10712	19980619
	JP 2001510154	T2	20010731	JP 2000-502767	19980619
	ZA 9806208	A	19990125	ZA 1998-6208	19980713
	US 6028063	A	20000222	US 1999-307517	19990507
	US 6180623	B1	20010130	US 1999-436057	19991108
	NO 9906352	A	20000313	NO 1999-6352	19991220
PRAI	US 1996-612680	A2	19960308		
	US 1997-796078	A2	19970205		
	US 1997-891833	A3	19970714		
	US 1998-45522	A3	19980321		
	WO 1998-US12769	W	19980619		
	US 1999-307517	A3	19990507		

OS MARPAT 129:67799

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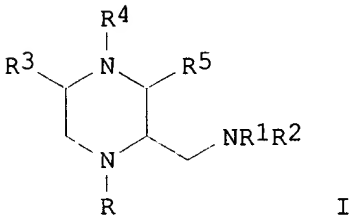

I

AB Title compds. [I; R = CO(CH2)nR6; R1,R2 = Me; R1R2 = (CH2)m, CH2CH(OH)CH2, CH2CH2OCH2CH2, etc.; R3,R5 = CH2NHSO2Me, CH2NHP(O)(OH)2, CH2OP(O)(OH)2, etc.; R4 = P(O)(OH)2, (CH2)pCO2H, CO2Me, etc.; R6 = (un)substituted (hetero)aryl; m = 4-8; n = 1-3; p = 0-20] were prepd. for treatment of **pruritus**. Thus, (R)-I (R = COCH2C6H3Cl2-3,4, NR1R2 = pyrrolidino, R3 = R5 = H, R4 = SO2Me) was prepd. Data for biol. activity of I were given.

L64 ANSWER 21 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:385518 HCAPLUS
DN 129:23446
TI **Antipruritic** agent
IN Nagase, Hiroshi; Utsumi, Jun; Endoh, Takashi; Tanaka, Toshiaki; Kamei, Junzo; Kawamura, Kuniaki
PA Toray Industries, Inc., Japan; Nagase, Hiroshi; Utsumi, Jun; Endoh, Takashi; Tanaka, Toshiaki; Kamei, Junzo; Kawamura, Kuniaki
SO PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DT Patent
LA Japanese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9823290	A1	19980604	WO 1997-JP4267	19971121 <--
	W: AU, CA, CN, JP, KR, NO, NZ, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2244256	AA	19980604	CA 1997-2244256	19971121 <--
	AU 9749683	A1	19980622	AU 1997-49683	19971121 <--
	AU 738743	B2	20010927		
	EP 897726	A1	19990224	EP 1997-912539	19971121 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				
	CN 1214634	A	19990421	CN 1997-193343	19971121 <--
	NO 9803431	A	19980924	NO 1998-3431	19980724 <--
	US 6174891	B1	20010116	US 1998-117052	19980824 <--
	US 6316461	B1	20011113	US 2000-615540	20000713 <--
PRAI	JP 1996-313476	A	19961125 <--		
	WO 1997-JP4267	W	19971121		
	US 1998-117052	A3	19980824		

OS MARPAT 129:23446

AB An **antipruritic** agent comprising an **opioid** . **kappa. receptor agonist** which is useful for the treatment of **pruritus** in various diseases accompanied by **pruritus**, morphinan quaternary ammonium salt derivs. and morphinan N-oxide derivs. Thus, 17-cyclopropylmethyl-3,14.beta.-dihydroxy-4,5.alpha.-epoxy-6.beta.-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan 2.0699 g was reacted with 1.3 mL Me iodide to give 17-cyclopropylmethyl-3,14.beta.-dihydroxy-4,5.alpha.-epoxy-17-methyl-6.beta.-[N-methyl-trans-3-(3-furyl]acrylamido)morphinan iodide 102 mg, which showed Ke value 16.67 nM in the presence of a .mu. antagonism naloxone (100 nM) for an ileum sample of guinea pig, and Ke value 14.18 nM in the presence of naloxone (30 nM) for a spermatic duct of a mouse.

L64 ANSWER 22 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:366889 HCAPLUS

DN 129:58790

TI anti-**pruritic .kappa.-agonist** pharmaceutical formulations and method of treating **pruritus** therewith

IN Farrar, John J.; **Chang, An-chih; Kumar, Virendra; Zhang, Wei Yuan;** Cowan, Alan

PA **Adolor Corp., USA**

SO U.S., 21 pp.
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5760023	A	19980602	US 1997-892599	19970714
	US 5869521	A	19990209	US 1998-64695	19980422
	WO 9903459	A1	19990128	WO 1998-US12789	19980619
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9884719	A1	19990210	AU 1998-84719	19980619
	AU 740566	B2	20011108		
	EP 996434	A1	20000503	EP 1998-935477	19980619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9810706	A	20000808	BR 1998-10706	19980619
	ZA 9806206	A	19990209	ZA 1998-6206	19980713
	US 6004964	A	19991221	US 1998-184393	19981102
	US 6048860	A	20000411	US 1999-411111	19991004

	NO 9906353	A	20000313	NO 1999-6353	19991220
	US 6156769	A	20001205	US 2000-488420	20000120
PRAI	US 1997-892599	A3	19970714		
	US 1998-64695	A	19980422		
	WO 1998-US12789	W	19980619		
	US 1998-184393	A3	19981102		
	US 1999-411111	A3	19991004		

OS MARPAT 129:58790
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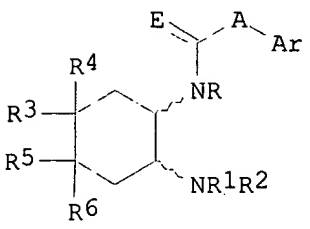

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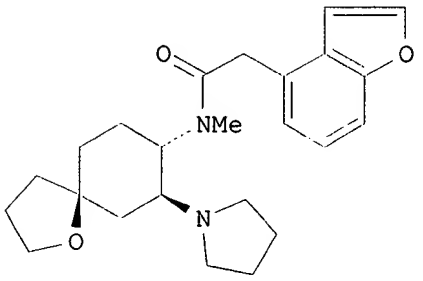


II

AB Anti-**pruritic** pharmaceutical formulations contg. **.kappa .-agonist** cyclohexanediamine derivs. I (A = bond, (CH2)q, CHMe, X(CH2)n; q = 1-4; n = 1-4; X = O, S; Ar = (un)substituted arom. hetero-arom., bicyclic-arom., tricyclic-arom., diphenylmethyl; R, R1, R2 independently are H, C1-3 alkyl, allyl; R1R2 may form a ring consisting of azetidinyl, pyrrolidinyl, 3-hydroxypyrrolidinyl, 3-fluoropyrrolidinyl, morpholinyl, piperidinyl, 3,4-dehydropiperidinyl; R3, R4, R5, R6 = H, OH, alkoxy, alkoxycarbonyl; R5R6 = ECH2CH2E; R5R6 may form a satd. 5-membered ring contg O, nitrogen, S, S(O), S(O)2; E = NOH, NOAc, O, S) were prepd. for prevention or treatment of **pruritus** in a mammal with the anti-**pruritic** formulations. Thus, the **antipruritic** activity was detd. by redn. of **scratching** of mice injected with II had 75% inhibition at 10 mg/kg s.c. Several pharmaceutical compns. of the compds. were mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration.

L64 ANSWER 23 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:331568 HCAPLUS
DN 129:614
TI Methods for treatment and prevention of drug-induced **pruritus** with serotonin type 3 receptor antagonists
IN Larijani, Ghassem E.
PA USA
SO U.S., 3 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5756514	A	19980526	US 1996-775455	19961230 <--

AB Methods are provided for treating and preventing **pruritus** induced by drugs (e.g. opioids or antibiotics) in patients by administration of a serotonin type 3 antagonist, e.g. ondansetron-HCl.

L64 ANSWER 24 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:141181 HCAPLUS
TI Arylacetamides as peripheral **kappa agonists.**
AU Marella, M.; Cortes-Burgos, L.; Daubert, J.; DeHaven, R.; DeHaven-Hudkins, D.; Gottshall, S.; Maycock, A.
CS **Adolor Corporation, Malvern, PA, 19355, USA**
SO Book of Abstracts, 215th ACS National Meeting, Dallas, March 29-April 2

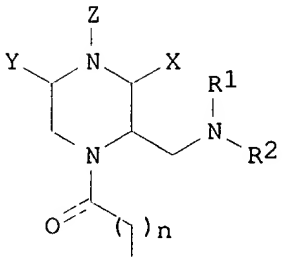
(1998), MEDI-151 Publisher: American Chemical Society, Washington, D. C.
CODEN: 65QTAA
DT Conference; Meeting Abstract
LA English
AB The therapeutic potential of **opioids** acting in the central nervous system(CNS) to alleviate pain is well established. **Opiate receptors** (.mu., **.kappa.**, and .delta.) are present in the central and peripheral nervous system of many species, including human. Antinociception in animals and humans can be produced by activation of these **receptors** within the CNS and there is mounting evidence that **opioid receptor**-mediated antinociception occurs in the periphery. Selective **.kappa. agonists** should be effective analgesics devoid of many side effects that are assocd. with .mu. **agonists**, such as respiratory depression, constipation, and phys. dependence. However, preclin. and clin. studies with centrally active **.kappa. agonists** have revealed undesired properties such as sedation, diuresis and dysphoria. Strategies at Adolor are to explore the peripherally acting **.kappa. receptor agonists** that have limited or no CNS access in an effort to reduce or eliminate these side effects. To achieve this goal, analogs of known centrally active **.kappa. agonists** such as ICI 199441 (1) have been structurally modified to give the compds. of the general structure (2) without any deleterious effects on the binding or selectivity to the **.kappa. receptor**. The syntheses, structure-activity relationships, and in vitro and in vivo data of these compds. will be presented.

L64 ANSWER 25 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:752779 HCAPLUS
DN 128:34783
TI **Kappa agonist** compounds (acylpiperazines and analogs) and pharmaceutical formulations thereof
IN Kruse, Lawrence I.; Chang, An-chih; Dehaven-Hudkins, Diane L.; Farrar, John J.; Gaul, Forrest; Kumar, Virendra; Marella, Michael Anthony; Maycock, Alan L.; Zhang, Wei Yuan
PA **Adolor Corp., USA**
SO U.S., 65 pp. Cont.-in-part of U.S. Ser. No. 612,680.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5688955	A	19971118	US 1997-796078	19970205
	US 5646151	A	19970708	US 1996-612680	19960308
	CA 2240728	AA	19970912	CA 1997-2240728	19970301
	AU 9721954	A1	19970922	AU 1997-21954	19970301
	AU 717126	B2	20000316		
	BR 9707958	A	20000104	BR 1997-7958	19970301
	US 5763445	A	19980609	US 1997-891833	19970714
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 5981513	A	19991109	US 1998-45522	19980321
	NO 9804107	A	19981109	NO 1998-4107	19980907
	US 6303611	B1	20011016	US 1998-150369	19980909
	US 6057323	A	20000502	US 1998-183011	19981030
	US 6028063	A	20000222	US 1999-307517	19990507
	US 6054445	A	20000425	US 1999-307387	19990507
	US 6239154	B1	20010529	US 1999-372191	19990811
	US 6180623	B1	20010130	US 1999-436057	19991108
	NO 2001004219	A	19981109	NO 2001-4219	20010831
	NO 2001004220	A	19981109	NO 2001-4220	20010831
PRAI	US 1996-612680	A2	19960308		
	US 1997-796078	A	19970205		
	WO 1997-US3353	W	19970301		
	US 1997-891833	A3	19970714		

	US 1997-899086	A3	19970723
	US 1998-34661	A2	19980303
	US 1998-45522	A3	19980321
	US 1998-150369	A2	19980909
	US 1998-183011	A3	19981030
	US 1999-307517	A3	19990507

OS MARPAT 128:34783
GI



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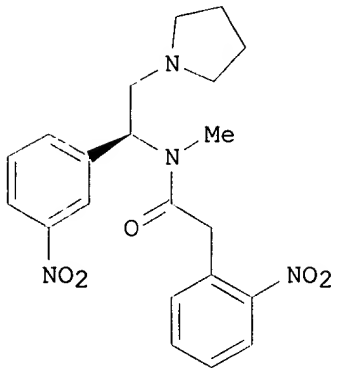


II

AB Compds. having **kappa opioid agonist** activity, compns. contg. them, and methods of using them as analgesics are provided. The compds. have 4 general structures, e.g., I [n = 1-3; R1 = R2 = Me; or NR1R2 forms various cyclic systems; Ar = (un)substituted Ph, benzothienyl, benzofuranyl, naphthyl, CHPh2, or 9-fluorenyl; Z = wide variety of sidechains; X, Y = various derivs. of CH2OH and CH2NH2]. A large no. of compds., as HCl salts and/or free bases, were prepd., tested, and/or claimed. For instance, title compd. II.HCl, i.e. ADL-01-0115-4, was prepd. in 51% yield by amidation of 2-nitrophenylacetic acid with the corresponding secondary amine using DCC and pyridine in CH2Cl2. In tests for displacement of [3H]-diprenorphin or [3H]-U-69593 from **kappa receptors** in vitro, II.HCl had Ki values of 35 and 3.2 nM, resp.

L64 ANSWER 26 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:616927 HCAPLUS
DN 127:283391
TI Pharmaceutical compositions containing film-forming **antihyperalgesic** opiates for treatment of hyperalgesic conditions
IN Farrar, John J.; Maycock, Alan L.; Kumar, Virendra; Balogh, Imre
PA **Adolor Corp., USA**
SO U.S., 11 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5667773	A	19970916	US 1996-614027	19960312
	CA 2223514	AA	19970918	CA 1997-2223514	19970226
	WO 9733634	A1	19970918	WO 1997-US3315	19970226
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9719847	A1	19971001	AU 1997-19847	19970226
	AU 715912	B2	20000210		
	EP 888141	A1	19990107	EP 1997-907990	19970226

R: DE, FR, GB
US 5888494 A 19990330 US 1997-891924 19970714
PRAI US 1996-614027 A 19960312
WO 1997-US3315 W 19970226
AB Topical anti-hyperalgesic film-forming compns. and methods of using compns. for the treatment of peripheral hyperalgesia comprise (a) **antihyperalgesic** opiates; (b) a film-forming polymeric material; and (c) an aq. pharmaceutically acceptable carrier. A pharmaceutical compn. contained loperamide.HCl 25.0, sodium carrageenan 25.0, calcium lactate 32.0, and water q.s. 100.0%.

L64 ANSWER 27 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:456146 HCAPLUS
DN 127:152946
TI Pharmaceutical formulations containing .**kappa**.-**opioid agonists**
IN Kruse, Lawrence I.; Kumar, Virendra; Chang, An-chih; Dehaven-Hudkins, Diane L.; Farrar, John J.; Maycock, Alan L.
PA **Adolor Corp.**, **USA**
SO U.S., 26 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	CA 2240728	AA	19970912	CA 1997-2240728	19970301
	WO 9732857	A1	19970912	WO 1997-US3353	19970301
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9721954	A1	19970922	AU 1997-21954	19970301
	AU 717126	B2	20000316		
	EP 885199	A1	19981223	EP 1997-914850	19970301
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				
	BR 9707958	A	20000104	BR 1997-7958	19970301
	US 5763445	A	19980609	US 1997-891833	19970714
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 5981513	A	19991109	US 1998-45522	19980321
	NO 9804107	A	19981109	NO 1998-4107	19980907
	US 6303611	B1	20011016	US 1998-150369	19980909
	US 6057323	A	20000502	US 1998-183011	19981030
	US 6028063	A	20000222	US 1999-307517	19990507
	US 6054445	A	20000425	US 1999-307387	19990507
	US 6239154	B1	20010529	US 1999-372191	19990811
	US 6180623	B1	20010130	US 1999-436057	19991108
	NO 2001004219	A	19981109	NO 2001-4219	20010831
	NO 2001004220	A	19981109	NO 2001-4220	20010831
PRAI	US 1996-612680	A2	19960308		
	US 1997-796078	A	19970205		
	WO 1997-US3353	W	19970301		
	US 1997-891833	A3	19970714		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
	US 1998-45522	A3	19980321		
	US 1998-150369	A2	19980909		
	US 1998-183011	A3	19981030		
	US 1999-307517	A3	19990507		

OS MARPAT 127:152946
AB Pharmaceutical formulations contg. .**kappa**.-**opioid agonists** (Markush structure given) are claimed. A capsule

contained active compd. 2.5, corn starch 23.0, lactose 145.0, talc 15.0, and magnesium stearate 3.0 g.

L64 ANSWER 28 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:332024 HCAPLUS
DN 126:308827
TI Peripherally active anti-hyperalgesic opiates
IN Yaksh, Tony L.; Farrar, John J.; **Maycock, Alan L.**; Lewis, Michael E.; Dow, Gordon J.
PA Regents of the University of California, USA; **Adolor Corporation** ; Yaksh, Tony L.; Farrar, John J.; Maycock, Alan L.; Lewis, Michael E.; Dow, Gordon J.
SO PCT Int. Appl., 317 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9709973	A2	19970320	WO 1996-US14727	19960912
	WO 9709973	A3	19970605		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG				
	US 5849761	A	19981215	US 1995-528510	19950912
	CA 2229814	AA	19970320	CA 1996-2229814	19960912
	AU 9670710	A1	19970401	AU 1996-70710	19960912
	AU 727982	B2	20010104		
	EP 852494	A2	19980715	EP 1996-931567	19960912
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
	BR 9610345	A	19990601	BR 1996-10345	19960912
	JP 11512438	T2	19991026	JP 1996-512136	19960912
	NO 9800700	A	19980512	NO 1998-700	19980219
	US 6166039	A	20001226	US 1998-199873	19981124
PRAI	US 1995-528510	A	19950912		
	WO 1996-US14727	W	19960912		

OS MARPAT 126:308827
AB Compns. and methods using the compns. for treatment of peripheral hyperalgesia are provided. The compns. contain an anti-hyperalgesia effective amt. of one or more compds. that directly or indirectly interact with peripheral **opiate receptors**, but that do not, upon topical or local administration, elicit substantial central nervous system effects. The anti-diarrheal compd. loperamide-HCl is preferred for use in the compns. and methods.

L64 ANSWER 29 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:719992 HCAPLUS
DN 126:211
TI Ondansetron: A review of its pharmacology and preliminary clinical findings in novel applications
AU Wilde, Michelle I.; Markham, Anthony
CS Adis International Limited, Auckland, N. Z.
SO Drugs (**1996**), 52(5), 773-794
CODEN: DRUGAY; ISSN: 0012-6667
PB Adis
DT Journal; General Review
LA English
AB A review with 185 refs. The use of ondansetron, a selective serotonin 5-HT3 **receptor** antagonist, is well established in patients with nausea and vomiting assocd. with cancer chemotherapy, radiotherapy or anesthesia and surgery. The wide distribution of 5-HT3 **receptors**

in the body and the role of these **receptors** in disease have provided the rationale for investigation of ondansetron in novel applications. Preliminary data have shown ondansetron to have clin. benefit in patients with nausea and vomiting assocd. with drug overdosage or poisoning, antiinfective or antidepressant therapies, uremia or neurol. trauma, and in patients with **pruritus**. Patients with gastrointestinal motility disorders (e.g. carcinoid syndrome, irritable bowel syndrome, diarrhea assocd. with cryptosporidiosis or diabetes, and chronic refractory diarrhea) have also shown some improvement when treated with ondansetron, as have patients with certain pain or CNS-related disorders [e.g. alc. (ethanol) dependence, **opiate** withdrawal, vertigo, cerebellar tremor and Parkinson's disease treatment-related psychosis]. In contrast to conventional antiemetics, ondansetron is generally well tolerated with a lower incidence of sedation and only isolated case reports of extrapyramidal reactions. Furthermore, unlike dopamine **receptor**-blocking neuroleptics, ondansetron does not appear to worsen the symptoms of Parkinson's disease. Thus, in addn. to its established indications, preliminary results suggest that ondansetron may be beneficial in a no. of novel applications. This drug may represent a treatment alternative in patients with refractory disease, or an effective treatment of conditions for which current therapies are either poorly tolerated or not available. Further investigation of ondansetron in a range of potential new applications appears to be warranted.

L64 ANSWER 30 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:654315 HCAPLUS
DN 125:298242
TI Pathophysiology of **itching**
AU Greaves, M. W.; Wall, P. D.
CS St John's Institute Dermatology, St Thomas' Hospital, London, SE1 7EH, UK
SO Lancet (**1996**), 348(9032), 938-940
CODEN: LANCAO; ISSN: 0140-6736
DT Journal; General Review
LA English
AB A review with 30 refs. **Itching** is the predominant symptom of skin disease but it is ill-understood and a challenge for future research. Even the major nerve pathways for **itch**, and its relation to pain are debatable. In inflamed skin, histamine plays a major role and its mode of release from mast cells in, for example, chronic urticaria is now better appreciated. Tachykinins including substance P and cytokines including interleukin-2 are evidently important peripherally. **Opioid** .mu.-**receptor**-dependent processes activate inhibitory circuits in the central nervous system and regulate the extent of intensity and quality of perceived **itch**. It is proposed that stimulation of large areas of skin such as by **scratching**, generates inhibitory activity which suppresses **itch** excitation. Therapeutic intervention based upon understanding these regulatory processes is a real prospect.

L64 ANSWER 31 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:236396 HCAPLUS
DN 124:307370
TI Naloxone versus nalbuphine infusion for prophylaxis of epidural morphine-induced **pruritus**
AU Kendrick, Will D.; Woods, Andrew M.; Daly, Martha Y.; Birch, Robert F. H.; DiFazio, Cosmo
CS Health Sciences Center, University Virginia, Charlottesville, VA, 22908, USA
SO Anesth. Analg. (Baltimore) (**1996**), 82(3), 641-7
CODEN: AACRAT; ISSN: 0003-2999
DT Journal
LA English
AB This randomized, double-blind study compared the efficacy of two .mu.-receptor antagonists, naloxone and nalbuphine, in the prophylactic management of **pruritus** in postcesarean section patients receiving epidural morphine. Dosages of study drugs were individualized

by the use of a patient self-administration (PSA) device. All 51 patients were healthy women who received a uniform epidural anesthetic and epidural morphine (5 mg). Coded solns. were infused for 24 h, with 5-min PSA lockout times: Group A (n = 17), nalbuphine 2.5 mg/h, PSA nalbuphine 1 mg; Group B (n = 16), naloxone 50 .mu.g/h, PSA saline; Group C (n = 18), naloxone 50 .mu.g/h, PSA naloxone 40 .mu.g. Patients were assessed for **pruritus** and pain every 8 h for 24 h. Both naloxone and nalbuphine provided good relief for **pruritus**; median pain and **pruritus** scores were in the none-to-mild range (0-3) for all groups at all assessment intervals. The **pruritus** scores of the PSA saline group were higher during the 16- to 24-h period ($P < 0.05$) than the scores of either group receiving .mu.-receptor antagonist by PSA. There was evidence of shortening of the duration of analgesia in patients receiving naloxone who required treatment for **pruritus** after 16 h. Patients who self-administered large doses of nalbuphine over the first 8 h also reported pain scores consistent with reversal of analgesia. The potency ratio for naloxone:nalbuphine for antagonism of the **pruritic** effects of epidural morphine was approx. 40:1. Intervention to treat either unrelieved **pruritus** or pain, resp., was necessary in the following nos. of patients: Group A, 0/1; Group B, 1/1; Group C, 2/2. Prophylactic infusions offer the potential for labor cost savings by minimizing the need for episodic therapeutic interventions to treat **pruritus**.

L64 ANSWER 32 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:865334 HCAPLUS
DN 123:306413
TI Microinjection of morphine into the rat medullary dorsal horn produces a dose-dependent increase in facial **scratching**
AU Thomas, David A.; Hammond, Donna L.
CS Department of Anesthesia and Critical Care, University of Chicago MC 4028, 5841 South Maryland Ave., Chicago, IL, 60637, USA
SO Brain Res. (**1995**), 695(2), 267-70
CODEN: BRREAP; ISSN: 0006-8993
DT Journal
LA English
AB It has been proposed that **opioids** act at the level of the medulla to produce facial **pruritus**. Supporting this hypothesis, microinjection of .mu.-**opioid receptor agonists** into the medullary dorsal horn (MDH; trigeminal subnucleus caudalis) of monkeys produces facial **scratching** behavior. The present study sought to establish a rodent model of **opioid**-induced facial **pruritus**. To this end, morphine (0.1, 0.3 or 1.0 .mu.g/0.2 .mu.l) or saline (0.2 .mu.l) was unilaterally microinjected into the MDH of male Sprague-Dawley rats. Behavior for the 20 min preceding and the 80 min after this microinjection was videotaped. Morphine produced dose-dependent increases in facial **scratching** behavior ipsilateral to the microinjections with the peak effect at 30-40 min after microinjection. Facial **scratching** continued for the entire 80 min post-microinjection test period. Morphine also produced a lesser degree of facial **scratching** contralateral to the microinjections. Increases in facial **scratching** ipsilateral to the microinjection of 0.3 .mu.g morphine into the MDH were attenuated by 0.4 mg/kg s.c. naloxone. These findings support the hypothesis that the MDH is a crit. site of action of **opioid agonists** in producing facial **pruritus**.

L64 ANSWER 33 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:749737 HCAPLUS
DN 123:159898
TI Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal
AU Egan, Talmage D.
CS Dep. Anesthesiology, Univ. Utah Sch. Med., Salt Lake City, UT, USA
SO Clin. Pharmacokinet. (**1995**), 29(2), 80-94
CODEN: CPKNDH; ISSN: 0312-5963

DT Journal; General Review
LA English
AB A review with 41 refs. Remifentanil is a novel, short-acting .mu.-**receptor opioid agonist** currently in the late stages of development. A member of the 4-anilidopiperidine class, it is unique among the currently marketed agents because of its ester structure. Remifentanil undergoes widespread extrahepatic metab. by blood and tissue nonspecific esterases, resulting in an extremely rapid clearance of approx. 3 L/min (180 L/h). Like the other members of this class of drugs, remifentanil is lipophilic and is widely distributed in body tissues with a steady-state vol. of distribution of approx. 30L. Because of its unique metabolic pathway (among this group of drugs) and rapid clearance, remifentanil represents a new pharmacokinetic class of **opioid**. Unlike the other fentanyl congeners, termination of the therapeutic effect of remifentanil mostly depends on metabolic clearance rather than on redistribution. The context-sensitive half-time [defined as the time necessary to achieve a 50% decrease in blood (or plasma) concn. after termination of a variable length, continuous infusion targeted to maintain a steady-state concn., where the 'context' is the duration of the infusion'] is strikingly short for remifentanil, and this is perhaps the most compelling evidence of the pharmacokinetic singularity of the drug. Detd. by computer simulation, the context-sensitive half-time of remifentanil is approx. 3 min, and is independent of infusion duration. Pharmacodynamically, remifentanil is similar to the other fentanyl congeners. The drug produces physiol. changes consistent with potent .mu.-**receptor agonist** activity, including analgesia and sedation. Its adverse effect profile (like that of the other drugs of this class) includes ventilatory depression, nausea, vomiting, muscular rigidity, bradycardia and **pruritus**. Because it does not release histamine upon injection, remifentanil has fewer hemodynamic adverse effects than morphine. The therapeutic potency of remifentanil is somewhat less than that of fentanyl, with an effective concn. (producing 50% of maximal effect, as measured by electroencephalog.) of approx. 15 to 20 .mu.g/L. Speed of onset of effect is very rapid and is similar to that of alfentanil, which is reflected in a t1/2keo (a parameter used to characterize the delay between peak blood drug concn. and peak pharmacodynamic effect utilising a theor. effect compartment) of approx. 1 to 2 min. Remifentanil is likely to be a welcome addn. to the anesthesia drug formulary. Anesthetists have long recognized the need for a short acting **opioid** with a predictable pharmacokinetic profile. Because the length of surgical procedures is often unpredictable, and because the level of surgical stimulation against which the depth of anesthesia must be balanced is highly variable and dynamic, the advantages of predictably short-acting agents are obvious.

L64 ANSWER 34 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:728598 HCAPLUS
DN 123:102497
TI Effects of naloxone infusions in patients with the **pruritus** of cholestasis: a double-blind, randomized, controlled trial
AU Bergasa, Nora Valeria; Alling, David W.; Talbot, Thomas L.; Swain, Mark G.; Yurdaydin, Cihan; Turner, Maria L.; Schmitt, Joseph M.; Walker, Elijah C.; Jones, E. Anthony
CS Nat. Inst. Health, Bethesda, MD, USA
SO Ann. Intern. Med. (**1995**), 123(3), 161-7
CODEN: AIMEAS; ISSN: 0003-4819
DT Journal
LA English
AB This is to det. whether endogenous **opioids** contribute to the **pruritus** of cholestasis by studying the effect of the **opiate** antagonist naloxone on the perception of **pruritus** and on **scratching** activity in patients with this form of **pruritus**. The design is a double-blind, placebo-controlled, crossover trial with four periods. 29 **Pruritic** patients were used with liver diseases of various causes. Each patient received as many as two naloxone and two placebo soln. infusions consecutively in random

order. During the infusions, visual analog scores of **pruritus** were recorded every 4 h while patients were awake; **scratching** activity independent of limb movements was recorded continuously. One patient had a mild reaction consistent with a naloxone-pptd. syndrome similar to **opiate** withdrawal. A significant 24-h rhythm of **scratching** activity was seen in 7 of 11 patients for whom complete 96-h data were collected. The mean of a visual analog score of the perception of **pruritus** (max., 10.0) recorded during naloxone infusions was 0.582 lower than that recorded during placebo infusions (95% Cl, 0.176 to 0.988; $P < 0.01$). The ratio of the geometric mean hourly **scratching** activity during naloxone infusions to that during placebo infusions was 0.727 (Cl, 0.612 to 0.842; $P < 0.001$) and was greater than 1.0 in only five patients. Naloxone administration is assocd. with amelioration of the perception of **pruritus** and redn. of **scratching** activity in cholestatic patients. Because of the **opioid receptor** specificity of the action of naloxone, these findings support the hypothesis that a mechanism underlying the **pruritus** of cholestasis is modulated by endogenous **opioids** and suggest that **opiate** antagonists may have a role in the management of this complication of cholestasis.

L64 ANSWER 35 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:691791 HCAPLUS
DN 121:291791
TI Alpha-2 agonists and analgesia
AU Eisenach, James C
CS Medical Center, Wake Forest University, Winston-Salem, NC, 27157-1009, USA
SO Expert Opin. Invest. Drugs (**1994**), 3(10), 1005-10
CODEN: EOIDER; ISSN: 0967-8298
DT Journal; General Review
LA English
AB A review, with 29 refs. In addn. to their anti-hypertensive effects, alpha-2 **agonists** also cause analgesia. Since analgesia from these drugs is due primarily to actions in the spinal cord, it is not surprising that analgesia is poor after systemic administration, but profound after injection near the cord (spinal or epidural administration). Advantages of alpha-2 **agonists** over **opioids** in the treatment of severe pain include lack of **opioid** type side effects (addiction, nausea, respiratory depression, **pruritus**), lack of abuse potential and efficacy in special situations where **opioids** fail (**opioid** tolerance, neuropathic pain, reflex sympathetic dystrophy). Clonidine, the lead compd. in this category, has been administered epidurally or spinally to over 1,000 patients in published reports, and detailed cerebrospinal fluid pharmacokinetics and pharmacodynamics have been described. Epidural clonidine has been designated as an orphan product in the US for the treatment of intractable cancer pain, and a multi-center, placebo-controlled, Phase III trial has demonstrated its safety and efficacy for this indication. As might be expected, epidural clonidine is effective in the setting of **opioid** tolerance, neuropathic pain and reflex sympathetic dystrophy, but is also effective alone and in combination with other analgesics in the treatment of postoperative and obstetric labor pain. Dexmedetomidine is the only other alpha-2 **agonist** under clin. development in injectable form. Although dexmedetomidine is a more potent and selective alpha-2 **agonist** than clonidine, its high lipid soly. leads to rapid systemic absorption after intraspinal use, which will probably lead to sedation and decreased blood pressure. Development of hydrophilic alpha-2 **agonists**, such as ST-91 and oxymetazoline, could offer unique advantages for this indication.

L64 ANSWER 36 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:261151 HCAPLUS
DN 120:261151
TI Multiple effects of morphine on facial **scratching** in monkeys
AU Thomas, David A.; Williams, Gene M.; Iwata, Koichi; Kenshalo, Daniel R.

Jr.; Dubner, Ronald
CS Neurobiol. Anesthesiol. Branch, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA
SO Anesth. Analg. (N. Y.) (**1993**), 77(5), 933-5
CODEN: AACRAT; ISSN: 0003-2999
DT Journal
LA English
AB The medullary dorsal horn (MDH), the medullary homolog of the spinal dorsal horn, is a site where **opioid-receptor agonists** can act at **opioid receptors** to produce pronounced facial **scratching**, the behavioral correlate of **pruritus**. In the present study, after a 10-min baseline period, morphine (5.0 .mu.g) was microinjected into the MDH of monkeys. Behavior was videotaped and facial **scratches** were counted by two independent raters. Morphine greatly increased facial **scratching** behavior, which is consistent with previous findings where .mu.-**opioid receptor agonists** microinjected into the MDH have been to induce dose-dependent, naloxone-reversible facial **scratching** in monkeys. In the current research, i.m. administration of the **opioid-receptor** antagonist, naloxone (0.5 mg/kg), reversed this MDH morphine-induced **scratching**. Addnl., i.m. morphine (1.0 mg/kg) produced a substantial redn. in facial **scratching** behavior. **Scratching** behavior continued at a high rate after injection of saline (0.1 mL/kg, i.m.). These findings support the hypothesis that morphine has both pruragenic and antipruragenic activity, depending on the site of action.

L64 ANSWER 37 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1994:154462 HCAPLUS
DN 120:154462
TI Noradrenergic and opioid systems interact to alter the detection of noxious thermal stimuli and facial **scratching** in monkeys
AU Thomas, David A.; Anton, Fernand; Kenshalo, Daniel R. Jr.; Williams, Gene M.; Dubner, Ronald
CS Neurobiol. Anesthesiol. Branch, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA
SO Pain (**1993**), 55(1), 63-70
CODEN: PAINDB; ISSN: 0304-3959
DT Journal
LA English
AB The authors examd. the ability of the .alpha.2-adrenoceptor **agonist**, ST-91, microinjected into the medullary dorsal horn (MDH), to diminish the sensory-discriminative features of noxious heat stimuli in awake behaving monkeys. Two monkeys performed a noxious thermal detection task and the time to detection of small increases in heat served as a measure of the perceived intensity of pain. ST-91 microinjected into the MDH (1.0, 3.0, 10.0 and 30.0 .mu.g/0.4 .mu.L) produced dose-dependent increases in detection time to graded temp. increases (0.4-1.0.degree.) from a noxious 46.degree. base line. These dose-dependent effects were attenuated by the systemic administration of the .alpha.2-adrenoceptor antagonist, idazoxan (2.0 mg/kg, i.m.), but not by the .alpha.1-adrenoceptor antagonist, prazosin (0.5 mg/kg, i.m.) or the **opioid-receptor** antagonist, naloxone (0.5 mg/kg, i.m.). The effect of ST-91 on detection latency of thermal stimuli was not the result of alterations in attentional, motivational or motoric aspects of the monkeys' behavior, because detection of visual stimuli and non-noxious temp. coolings (36.0-34.5.degree.) in a similar paradigm were not consistently altered. Microinjection of morphine (3.0 mg) into the MDH also increased detection latency of the noxious heat stimuli. Systemic administration of the **opioid-receptor** antagonist, naloxone (0.5 mg/kg), and the .alpha.2-adrenoceptor antagonist, idazoxan (2.0 mg/kg, i.m.) attenuated these effects of morphine. In a sep. expt., morphine (5.0 .mu.g) microinjected into the MDH induced facial **scratching** behavior. Idazoxan (2.0 mg/kg) was effective at attenuating this **scratching** behavior. The authors have thus

shown participation of MDH .alpha.2-adrenoceptors in the process underlying the perception of the intensity of noxious thermal stimulation in monkeys. Further, **opioid** and noradrenergic systems interacted in the noxious heat detection paradigm and a paradigm where facial **scratching** behavior was studied.

L64 ANSWER 38 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:641300 HCAPLUS
DN 119:241300
TI The medullary dorsal horn. A site of action of morphine in producing facial **scratching** in monkeys
AU Thomas, David A.; Williams, Gene M.; Iwata, Koichi; Kenshalo, Daniel R., Jr.; Dubner, Ronald
CS Neurobiol. Anesthesiol. Branch, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA
SO Anesthesiology (**1993**), 79(3), 548-54
CODEN: ANESAV; ISSN: 0003-3022
DT Journal
LA English
AB **Pruritus** is a common side effect of epidural and intrathecal morphine administration in humans. This naloxone-reversible **pruritus** is typically present on the trunk, but is often severe around the eyes and nose, of the patients. The brain stem was proposed as the site where **opioids** act to produce this effect. The authors studied the effect of morphine administered into the medullary dorsal horn (MDH), the brain stem homolog of the spinal dorsal horn, on facial-**scratching** behavior in monkeys. Morphine was unilaterally microinjected into the MDH of rhesus monkeys. Systemic injections of the **opioid-receptor** antagonist naloxone (0.5 mg/kg i.m.) were also made in combination with morphine microinjection. Systemic injections of the antihistamine chlorcyclizine (1.0 and 2.5 mg/kg i.m.) were also made to det. if facial **scratching** was mediated through histamine release. The monkeys were videotaped for 10-15 min before and 1-2 h after **opioid** microinjection, and he no. and location of **scratches** were counted. A dose-response curve was established for the .mu./.delta.-**opioid-receptor agonist** morphine (0.5, 1.0, 2.5, and 5.0 .mu.g). Specificity of the site of action within the MDH was examd. by systematically changing the microinjection site, and examg. the area of the face that the monkeys **scratched**. Morphine produced large dose-dependent increases in facial **scratching** ipsilateral to the microinjection. Increases in facial **scratching** were also obsd. contralateral to the microinjections. These effects were reversed by naloxone. The facial area **scratched** after microinjection of morphine was directly related to the injection site, with 1-mm changes in the location of the microinjection resulting in pronounced changes in the area of the face that the monkeys **scratched**. Systemic injection of chlorcyclizine produced only a small, transient attenuation of morphine's effect. Data from this study demonstrate that the MDH is a site where morphine acts to produce facial **scratching** in monkeys by acting at **opioid receptors**. Also probably the MDH is a site where centrally administered **opioids** act in producing facial **pruritus** in humans. The effects of morphine on facial-**scratching** behavior were only modestly attenuated with chlorcyclizine, indicating a minor involvement of a histamine-dependent mechanism of action.

L64 ANSWER 39 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:400816 HCAPLUS
DN 119:816
TI Pharmacologic characteristics of a **medullary hyperalgesic center**
AU Parvini, Shirin; Hamann, Scott R.; Martin, William R.
CS Dep. Pharmacol. Anesthesiol., Univ. Kentucky, Lexington, KY, USA
SO J. Pharmacol. Exp. Ther. (**1993**), 265(1), 286-93
CODEN: JPETAB; ISSN: 0022-3565

DT Journal
LA English
AB The effects of ethylketazocine, U-50,488, morphine and (-)-nicotine administered both i.p. and into the mid-fourth ventricle of intact rats were investigated using a conventional high intensity tail-flick reflex and one evoked with a lower intensity thermal stimulus. The sensitivity of the low intensity thermally evoked tail avoidance reflex was several times that of a high intensity tail-flick reflex in detecting the analgesic activity of morphine and yielded valid assays and relative potencies between morphine, EKC (18.76) and U-50,488 (0.23) when the drugs were administered i.p. When the **opioid** drugs were administered into the fourth ventricle they produced a dose-related shortening of the latency of the low intensity thermally evoked tail avoidance reflex. (-)-Nicotine, when administered into the mid-fourth ventricle, produced analgesia in low doses and hyperalgesia in high doses. Naltrexone and mecamylamine, when administered into the fourth ventricle, produced a dose-related analgesia. Doses of naltrexone and mecamylamine which antagonize maximally hyperalgesic doses of (-)-nicotine and ethylketazocine did not produce analgesia; however, larger doses produced analgesia. These observations suggest that analgesic doses do not involve prototypic .**kappa**.-**opioidergic** or nicotinic mechanisms. These data confirm the existence of a medullary hyperalgesic center which may have both .mu.- and .**kappa**.-**opioidergic** as well as nicotinic mechanisms. Furthermore, these data indicate that this medullary hyperalgesic mechanism may have spontaneous or evoked tone and provide an explanation for the analgesic action of naltrexone and mecamylamine.

L64 ANSWER 40 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:543892 HCAPLUS
DN 117:143892
TI Effects of central administration of opioids on facial **scratching** in monkeys
AU Thomas, D. A.; Williams, G. M.; Iwata, K.; Kenshalo, D. R., Jr.; Dubner, R.
CS Neurobiol. Anesthesiol. Branch, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA
SO Brain Res. (**1992**), 585(1-2), 315-17
CODEN: BRREAP; ISSN: 0006-8993
DT Journal
LA English
AB Epidural and intrathecal administration of **opioids** to humans can produce facial **pruritus** and **scratching** that is naloxone reversible. It has been proposed that **opioids** may act at the level of the medulla to produce facial **pruritus** and assocd. **scratching** behavior. The effects of .mu., .delta. and .**kappa**. **opioid-receptor agonists** microinjected unilaterally into the medullary dorsal horn (MDH) on facial **scratching** was investigated in cynomologus monkeys. The selective .mu. **opioid-receptor agonist**, DAMGO (3.1-25.0 ng) produced large dose-dependent, naloxone-reversible increases in facial **scratches**. The selective .delta. **opioid-receptor agonist**, DPDPE (1.0-5.0 .mu.g) and the selective .**kappa**. **opioid-receptor agonist**, U-50,488H (0.1-5.0 .mu.g) did not produce significant increases in facial **scratching** behavior. Thus, the MDH is a site where DAMGO, a .mu. **opioid-receptor agonist**, can act to produce facial **scratching** in monkeys, and the MDH is likely to site where centrally administered **opioids** act to produce facial **pruritus** in humans.

L64 ANSWER 41 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:208091 HCAPLUS
DN 116:208091
TI Characterization of intrathecal vasopressin-induced antinociception, **scratching** behavior, and motor suppression

AU Thurston, Cindy L.; Campbell, Ian G.; Culhane, E. S.; Carstens, E.; Watkins, L. R.
CS Dep. Anim. Physiol., Univ. California, Davis, CA, 95616, USA
SO Peptides (Fayetteville, N. Y.) (**1992**), 13(1), 17-25
CODEN: PPTDD5; ISSN: 0196-9781
DT Journal
LA English
AB Intrathecal (IT) administration of vasopressin (VP) produces antinociception, **scratching** behavior, and motor suppression. The present expts. characterized these effects with regards to the following: (1) VP **receptor** specificity, (2) possible involvement of endogenous **opiates**, (3) possible involvement of seizure activity, and (4) whether the antinociception is due to direct actions of VP at the spinal cord. These studies showed that IT administration of a V1-specific vasopressin antagonist completely blocked the antinociception, **scratching** behavior, and motor suppression produced by 25 ng IT vasopressin. Furthermore, IT administration of the vasopressin metabolite, [pGlu4,Cyt6]AVP(4-9), produced none of the effects produced by vasopressin. Systemic administration of the **opiate** antagonists naloxone (1 mg/kg i.p.) and naltrexone (10 mg/kg i.p.) had no significant effect on the antinociception produced by IT vasopressin, whereas naltrexone potentiated the **scratching** behavior. Neither the IT vasopressin-induced antinociception nor **scratching** behavior was affected by pretreatment with the anticonvulsant sodium valproate. In addn., IT vasopressin inhibited the tail flick reflex in rats with transected spinal cords, demonstrating direct spinal effects of vasopressin. In conclusion, IT administration of vasopressin produces antinociception, **scratching** behavior, and motor suppression via activation of VP-specific **receptors** in the spinal cord.

L64 ANSWER 42 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:51930 HCAPLUS
DN 116:51930
TI Neuromedin-induced excessive grooming/**scratching** behavior is suppressed by naloxone, neurotensin and a dopamine D1 receptor antagonist
AU Van Wimersma Greidanus, Tjeerd B.; Maigret, Carla
CS Rudolf Magnus Inst., Univ. Utrecht, Utrecht, 3521 GD, Neth.
SO Eur. J. Pharmacol. (**1991**), 209(1-2), 57-61
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Neuromedin B and neuromedin C were tested for their grooming/**scratching**-inducing effects and the compn. of neuromedin-induced grooming was established by calcg. the relative contribution of various grooming elements to the total grooming scores. Excessive grooming induced by neuromedins is characterized by a predominant display of **scratching**. Since neuromedin C is much more potent than meuromedin B in inducing excessive grooming/**scratching** behavior, it is concluded that the carboxyl-terminal heptapeptide of neuromedin C is important for this effect. Furthermore, it is concluded that dopamine D1 **receptors** and **opiate receptors** are involved in this effect since the dopamine D1 **receptor** antagonist, SCH 23390, as well as the **opiate receptor** antagonist, naloxone, suppresses or attenuates neuromedin C-induced excessive grooming/**scratching** behavior.

L64 ANSWER 43 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:422621 HCAPLUS
DN 115:22621
TI .**kappa**.- And .delta.-**opioids** block **sympathetically** dependent hyperalgesia
AU Taiwo, Yetunde O.; Levine, Jon D.
CS Dep. Anat. Med., Univ. California, San Francisco, CA, 94143-0724, USA
SO J. Neurosci. (**1991**), 11(4), 928-32
CODEN: JNRSDS; ISSN: 0270-6474
DT Journal

LA English
AB Direct hyperalgesia induced by PGE2 can be blocked by .mu.- but not .delta.- or .**kappa**.-**opioids**. However, there is evidence that .**kappa**.- and .delta.-**opioid receptors** are located on sympathetic postganglionic neuron (SPGN) terminals, which mediate bradykinin (BK) hyperalgesia via SPGN-terminal-dependent prodn. of PGE2. Therefore, the antinociceptive effects of .delta.- and .**kappa**.-**opioids** on BK hyperalgesia were evaluated. It was demonstrated that the mech. hyperalgesia induced by intradermal injection of BK can be blocked by the .**kappa**.-**opioid agonist** U 50,488H and by the .delta.-**opioid agonist** (D-Pen2,5)-enkephalin (DPDPE), as well as the .mu.-**opioid agonist** Tyr-D-Ala-Gly-NMe-Phe-Gly-ol (DAMGO). Pertussis toxin prevented the inhibition of BK-induced hyperalgesia by U 50,488H, DPDPE, or DAMGO. The obsd. peripheral analgesic effects of .**kappa**.- and .delta.-**opioid agonists** result from actions upon SPGN terminals and these effects are mediated by inhibitory G-proteins.

L64 ANSWER 44 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1990:132682 HCAPLUS
DN 112:132682
TI **Opioid** inhibition of kainic acid-induced **scratching**: mediation by mu and sigma but not delta and **kappa receptors**
AU Kellstein, David E.; Coghill, Robert C.; Frenk, Hanan; Bossut, Daniel F.; Mayer, David J.
CS Med. Coll. Virginia, Virginia Commonw. Univ., Richmond, VA, 23298, USA
SO Pharmacol., Biochem. Behav. (**1990**), 35(1), 1-5
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
AB **Scratching** induced by intrathecal (IT) administration of kainic acid (0.5 nmol) to rats was inhibited by IT pretreatment with the selective .mu. **agonists** levorphanol (30 and 90 nmol), [D-Ala2,N-Met-Phe4,Gly5-ol]-enkephalin (DAGO)(0.4 and 1.1 nmol), or morphine (90 nmol), the mixed .mu.-.delta. **agonist** [D-Ala2,D-Leu5]-enkephalinamide (DADLE)(10 and 30 nmol), or the .sigma./phencyclidine (PCP) **agonists** dextrorphan (90 nmol) or (+)-N-allyl-N-normetazocine ([+]-NAM)(90 nmol). The .**kappa**. **agonists** dynorphin (1.1 nmol) and ethylketocyclazocine (90 nmol) had no significant effect, nor did the selective .delta. **agonist** [D-Pen2,D-Pen5]-enkephalinamide (DPDPE)(90 nmol). The nonopioids (+)-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine ([+]-3-PPP, 90 nmol) and PCP (90 nmol), selective for .sigma. and PCP sites, resp., both antagonized kainic-induced **scratching**. Levorphanol- and DADLE-induced attenuation of **scratching** was partially antagonized by naltrexone. These findings suggest that **opioid** inhibition of kainic acid-induced **scratching** is mediated by classical .mu. **receptors** as well as .sigma. and PCP sites.

L64 ANSWER 45 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1989:51239 HCAPLUS
DN 110:51239
TI Intrathecal **injection** of a .**kappa**. **opioid agonist** produces hyperalgesia in the guinea pig
AU Leighton, G. E.; Hill, R. G.; Hughes, J.
CS Parke-Davis Res. Unit., Addenbrookes Hosp., Cambridge, UK
SO Eur. J. Pharmacol. (**1988**), 157(2-3), 241-2
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB The .**kappa**.-**opioid agonist** U-69593 at 30 .mu.g intrathecally in the lumbar region reduced the nociceptive threshold in guinea pigs in a paw-pressure test. This effect was seen in 5 min, peaked at 15 min, and was gone by 30 min. Pretreatment with naloxone

abolished this hyperalgesia.

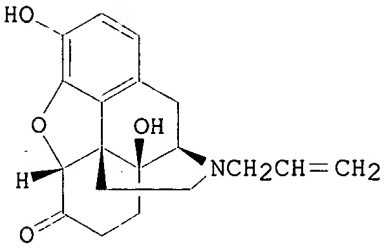
L64 ANSWER 46 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1987:13014 HCAPLUS
DN 106:13014
TI **Itch** and endorphins
AU Haegermark, O.
CS Dep. Dermatol., Karolinska Sjukhuset, Stockholm, 104 01, Swed.
SO New Trends Allergy 2, [Pap. Int. Symp.] (**1986**), Meeting Date 1985, 128-34. Editor(s): Ring, Johannes; Burg, Guenter. Publisher: Springer, Berlin, Fed. Rep. Ger.
CODEN: 55GXAT
DT Conference; General Review
LA English
AB A review, with 26 refs., on the involvement of endorphin [60118-07-2]s and **opiate receptors** in the transmission of **pruritis** both at peripheral and central levels and on the **itch**-relieving effects of naloxone.

L64 ANSWER 47 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1986:179629 HCAPLUS
DN 104:179629
TI In **vivo studies** on **kappa opioid receptors**
AU Cowan, Alan; Gmerek, Debra E.
CS Sch. Med., Temple Univ., Philadelphia, PA, 19140, USA
SO Trends Pharmacol. Sci. (**1986**), 7(2), 69-72
CODEN: TPHSDY; ISSN: 0165-6147
DT Journal; General Review
LA English
AB Various in vivo tests for the screening of agents with .**kappa**.-**opioid** activity are surveyed. Special emphasis is placed on a bombesin [31362-50-2]-induced **scratch** test in rats; other procedures include diuresis and increased food intake in rats and nalorphine discrimination and morphine withdrawal in monkeys. These tests are designed to assist in the optimization of the activity of **opioid** analgesics at the various **opioid receptors**.

L64 ANSWER 48 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1986:62438 HCAPLUS
DN 104:62438
TI Hyperalgesia mediated by **peripheral opiate receptors** in the rat
AU Van der Kooy, Derek; Nagy, James I.
CS Dep. Anat., Univ. Toronto, Toronto, ON, M5S 1A8, Can.
SO Behav. Brain Res. (**1985**), 17(3), 203-11
CODEN: BBREDI; ISSN: 0166-4328
DT Journal
LA English
AB The responses of rats to noxious chem. stimuli applied to the ear (ear **scratch** test) were measured after local pretreatment of these areas with etorphine [14521-96-1]. Local etorphine administration produced a low-dose hyperalgesia and high-dose analgesia. Local as opposed to systemic effects of etorphine were inferred from the absence of effects on the contralateral vehicle-treated ear. Systemic administration of naloxone or of a quaternary **opiate** antagonist (MRZ 2663-BR), which is relatively ineffective in crossing the blood-brain barrier, blocked the low-dose hyperalgesic effect of etorphine in the ear **scratch** test. As a test for the putative hyperalgesic function of peripheral sensory nerve **opiate receptors**, neonatal rats were treated with capsaicin (50 mg/kg s.c.) to destroy specifically the subpopulation of primary sensory neurons on which the peripheral **opiate receptors** are thought to be located, without markedly altering pain thresholds. As adults, these neonatally treated rats showed potentiated analgesic responses to systemic morphine

[57-27-2], as would be predicted by central analgesic **opiate receptors** now acting without opposition from peripheral hyperalgesic **opiate receptors**. Thus, **opiate receptors** on primary sensory neurons may mediate hyperalgesic functions, and endogenous **opioids** might normally play a role in the peripheral induction of irritation, inflammation, and pain reactions.

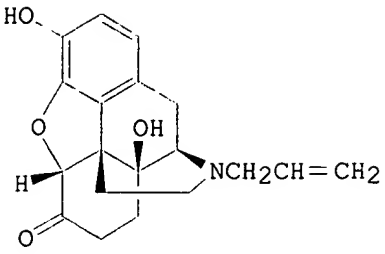
L64 ANSWER 49 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1982:608198 HCAPLUS
DN 97:208198
TI Behavioral alterations produced by chronic naloxone **injections**
AU Malin, David H.; Layng, Michael P.; Swank, Paul; Baker, Melanie J.; Hood, Joyce L.
CS Univ. Houston, Houston, TX, 77058, USA
SO Pharmacol., Biochem. Behav. (**1982**), 17(3), 389-92
CODEN: PBBHAU; ISSN: 0091-3057
DT Journal
LA English
GI



I

AB Repeated blockade of the endorphin **receptors** by naloxone (I) [465-65-6] (0.6 mg/kg twice daily for 6 days, s.c.) eventually induces symptoms resembling an **opiate** abstinence syndrome, despite the complete absence of **opiate** narcotics. Body shakes, head shakes, **scratches** and total symptoms were significantly elevated after I treatment. Symptoms were completely reversed by a small dose of morphine [57-27-2] but not by naloxone. In a 2nd expt., rats were injected for 10 days with the same dosage of naloxone. The abstinence-like syndrome began after 6 days of naloxone and continued for several days after cessation of injections. Total symptoms, body shakes, **scratches** and aggression were significantly elevated over controls and were reversed by morphine but not by naloxone.

L64 ANSWER 50 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1982:97588 HCAPLUS
DN 96:97588
TI **Antipruritic** effect of an opiate antagonist, naloxone hydrochloride
AU Bernstein, Joel E.; Swift, Robert M.; Soltani, Keyoumars; Lorincz, Allan L.
CS Pritzker Sch. Med., Univ. Chicago, Chicago, IL, USA
SO J. Invest. Dermatol. (**1982**), 78(1), 82-3
CODEN: JIDEAE; ISSN: 0022-202X
DT Journal
LA English
GI



I

AB Central elicitation of **itch** by morphine [57-27-2] may result from binding to **opiate receptors**, mimicking the physiol. binding of endorphins and enkephalins to these **receptors**. Pretreatment of normal subjects with naloxone (I) [465-65-6] resulted in a diminution or abolition of histamine-provoked **itch**. Apparently, central **opioid** peptides are mediators of the **itch** sensation. Naloxone and related **opiate** antagonists may be useful in the treatment of various **pruritic** disorders.

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L90 ANSWER 1 OF 1 EMBASE
AN 92254270 EMBASE
DN 1992254270
TI Effects of central administration of **opioids** on **facial scratching** in monkeys.
AU Thomas D.A.; Williams G.M.; Iwata K.; Kenshalo Jr. D.R.; Dubner R.
CS Neurobiology/Anesthesiology Branch, National Inst. of Dental Research, National Institutes of Health,Bethesda, MD 20892, United States
SO Brain Research, (1992) 585/1-2 (315-317).
ISSN: 0006-8993 CODEN: BRREAP
CY Netherlands
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Epidural and intrathecal administration of **opioids** to humans can produce facial **pruritus** and **scratching** that is naloxone reversible. It has been proposed that **opioids** may act at the level of the medulla to produce facial **pruritus** and associated **scratching** behavior. We investigated the effects of .mu., .delta. and .**kappa**. **opioid-receptor agonists** microinjected unilaterally into the medullary dorsal horn (MDH) on **facial scratching** in cynomologus monkeys. The selective .mu. **opioid-receptor agonist**, DAMGO (3.1-25.0 ng) produced large dose-dependent, naloxone-reversible increases in facial **scratches**. The selective .delta. **opioid-receptor agonist**, DPDPE (1.0-5.0 .mu.g) and the selective .**kappa**. **opioid-receptor agonist**, U-50,488H (0.1-5.0 .mu.g) did not produce significant

increases in **facial scratching** behavior. We conclude that the MDH is a site where DAMGO, a .mu. **opioid-receptor agonist**, can act to produce **facial scratching** in monkeys, and that the MDH is likely the site where centrally administered **opioids** act to produce facial **pruritus** in humans.
CT Medical Descriptors:
*brain stem
***pruritus**
animal experiment
article
controlled study
dose response
intracerebral drug administration
male
monkey
nonhuman
priority journal
regional perfusion
Drug Descriptors:
***opiate receptor**
***receptor subtype**
*3,4 dichloro n methyl n [2 (1 pyrrolidinyl)cyclohexyl]benzeneacetamide methanesulfonate: PD, pharmacology
*3,4 dichloro n methyl n [2 (1 pyrrolidinyl)cyclohexyl]benzeneacetamide methanesulfonate: CM, drug comparison
*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: PD, pharmacology
*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: IT, drug interaction
*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: CB, drug combination
*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: DO, drug dose
*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: CM, drug comparison
*enkephalin[2,5 dextro penicillamine]: PD, pharmacology
*enkephalin[2,5 dextro penicillamine]: CM, drug comparison
naloxone: IT, drug interaction
naloxone: CB, drug combination
RN (3,4 dichloro n methyl n [2 (1 pyrrolidinyl)cyclohexyl]benzeneacetamide methanesulfonate) 83913-06-8; (enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]) 78123-71-4; (enkephalin[2,5 dextro penicillamine]) 88373-73-3, 88381-29-7; (naloxone) 357-08-4, 465-65-6
CN U 50488h
CO Sigma (United States)

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L108 ANSWER 1 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-599819 [68] WPIX
DNC C2001-177425
TI New **itching** inhibitor containing morphinan derivative for cornea or conjunctiva.
DC B02
PA (TORA) TORAY IND INC
CYC 1
PI JP 2001163784 A 20010619 (200168)* 13p A61K031-485
ADT JP 2001163784 A JP 1999-345898 19991206
PRAI JP 1999-345898 19991206
IC ICM A61K031-485
ICS A61P027-02
ICA C07D489-08
AB JP2001163784 A UPAB: 20011121
NOVELTY - New **itching** inhibitor for cornea or conjunctiva comprises morphinan derivative or its pharmacologically acceptable acid salts as active ingredient.
DETAILED DESCRIPTION - New **itching** inhibitor for cornea or conjunctiva comprises morphinan derivative of formula (I) or its pharmacologically acceptable acid salts as active ingredient.
... = double or single bond;
R1 = 1-5C alkyl, 4-7C cycloalkyl, 5-7C cycloalkenylalkyl, 6-12C aryl, 7-13C aralkyl, 4-7C alkenyl, allyl, 1-5C furan-2-alkyl or 1-5C thiophenyl-2-alkyl;
R2 = H, OH, NO2, 1-5C alkanoyloxy, 1-5C alkoxy, 1-5C alkyl or -NR9R10;
R3 = H, hydroxy, 1-5C alkanoyloxy, 1-5C alkoxy;
R9 = H or 1-5C alkyl;
R10 = H, 1-5C alkyl or C(O)R11;
R11 = H, phenyl or 1-5C alkyl;
A = -XC(=Y)-, -XC(=Y)Z-, -X- or -XSO2-;
X,Y or Z = NR4, S or O;
R4 = H, 1-5C alkyl, 6-12C aryl;
B = valence bond, 1-14C alkylene (optionally substituted with 1-5C alkoxy, 1-5C alkanoyloxy, hydroxy, F, Cl, BR. I, amino, NO2, CN, CF3 or phenoxy and 1-3 methylenes can be placed by carbonyl), 2-14C acyclic unsaturated hydrocarbon having 1 to 3 double bond and/or triple bond, thioether bond, 1-14C hydrocarbon having 1 to 5 ether bond and/or amino bond;
R5 = H or phenyl, naphthyl, fluorenyl, pyridyl, quinolinyl, isoquinolinyl or a group of formula (i)-(iv);
Q = N, O or S;
T = CH, N, O or S;
I = 0-5;
m, n = 0-5; and
m+n = 0-5;
R6 = H;
R7 = H, hydroxy, 1-5C alkoxy or 1-5C alkanoyloxy;
R6 + R7 = -O-, -CH2- or -S-;
R8 = H, 1-5C alkyl or 1-5C alkanoyl.
An INDEPENDENT CLAIM is also included for **itching** inhibitor for cornea or conjunctiva comprising morphinan quaternary ammonium derivative of formula (II) or morphinan-N-oxide derivative of formula (III) or its acid salts as active ingredient.
R1 = 1-5C alkyl, 4-7C cycloalkyl, 5-7C cycloalkenylalkyl, 7-13C aralkyl, 4-7C alkenyl, allyl, preferably methyl, ethyl, propyl, butyl, isobutyl, cycloproylmethyl, allyl, benzyl or phenthyl;
R2 = H, OH, NO2, 1-5C alkanoyloxy, 1-5C alkoxy, 1-5C alkyl, preferably H, OH, acetoxy or methoxy;
R3 = H, hydroxy, 1-5C alkanoyloxy, 1-5C alkoxy, preferably H, OH, acetoxy or methoxy;

R4 = H, 1-5C alkyl, 6-12C aryl, preferably H or 1-5C alkyl;
A = 1-6C alkylene, C=C, C equivalent to C;
R5 = H or phenyl, naphthyl, fluorenyl, pyridyl, quinolinyl, isoquinolinyl or a group of formula (i)-(iv), preferably phenyl or (i);
X = counter ion.

ACTIVITY - Antipruritic; Ophthalmological.

MECHANISM OF ACTION - Opioid kappa receptor agonist.

(-)-17-(Cyclopropylmethyl)-3,14- beta -dihydroxy-4,5- alpha -epoxy-6-beta -(N-methyl-trans-3-(3- furyl)acrylamide)morphinan hydrochloride of formula (Ia) was dissolved in saline to prepare 0.1 micro gram/ml solution. The obtained solution (20 ml) (2 mg/site) was administered on the right eye of Hartley guinea pig. 30 minutes later, histamine solution (5 mg/site) was administered on the right eye, and saline (20 ml) was administered on the left eye. For the next 30 minutes, guinea pig was filmed by a video camera to observe its scratching activity. The results showed that the compound (29) significantly inhibited itching induced by histamine.

USE - Itching inhibitor is used for the treatment of itching caused by corneal ulcer, bacterial keratitis, viral keratitis, keratomycosis, lamellar keratitis, xerophthalmia, dry eye, keratoconjunctivitis sicca, infectious keratoconjunctivitis, allergic conjunctivitis, vernal conjunctivitis, phlyctenular conjunctivitis, follicular conjunctivitis, conjunctivitis of Stevens-Johnson syndrome, conjunctivitis of pemphigoid, dacryocystitis or hordeolum.

ADVANTAGE - The inhibitor is effective for reducing itching due to its opioid kappa receptor agonistic compound.

Dwg.0/1

FS CPI
FA AB; GI; DCN
MC CPI: B06-D03; B06-H; B14-N03; B14-N17

L108 ANSWER 2 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-441332 [47] WPIX
DNN N2001-326505 DNC C2001-133243
TI New metallopeptides which are specific for **opioid receptors**, are useful in treatment of e.g. pain, drug addiction, autoimmune disorders or inflammation, or for appetite suppression.
DC B04 P34
IN HUI-ZHI, C; SHARMA, S D; WEI, Y
PA (PALA-N) PALATIN TECHNOLOGIES INC
CYC 94
PI WO 2001036006 A1 20010525 (200147)* EN 52p A61K051-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001016238 A 20010530 (200152) A61K051-00
ADT WO 2001036006 A1 WO 2000-US31797 20001117; AU 2001016238 A AU 2001-16238 20001117
FDT AU 2001016238 A Based on WO 200136006
PRAI US 1999-166582P 19991119
IC ICM A61K051-00
ICS A61M036-14
AB WO 200136006 A UPAB: 20011129
NOVELTY - Peptides, and libraries of these, which include a metal ion-binding domain (MIBD), and which are specific for **opioid receptors** when complexed with a metal ion, are described.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a construct comprising a MIBD comprising two or more linked amino acid residues (AARs) which form a nitrogen-containing and sulfur-containing ligand available for complexing with a metal ion. The construct is conformationally restrained in a structure which is specific for one or more **opioid receptors** upon complexing the MIBD with a metal ion;

(2) a manufactured peptide, and its salts, which comprises a MIBD comprising two or more contiguous amino acids an a determined biological-function domain (BFD) specific for one or more **opioid receptors**. At least a portion of the BFD is co-extensive with at least a portion of the MIBD. The BFD is conformationally restrained upon complexing the MIBD with a metal ion;

(3) a combinatorial library targeted to **opioid receptors** of different sequence peptide members or peptidomimetic sequence synthesized on a solid phase (SP), where each library member comprises a peptide sequence or peptidomimetic sequence of 3 or more AARs (and/or mimics of these) bound to the SP. This sequence comprises (a) a sequence of 2 or more AARs (and/or mimics) which form a MIBD and which include at least one amino acid residue (and/or mimic) containing at least one S atom which is protected by an orthogonal S-protecting group; (b) a sequence of one or more AARs (and/or mimics) at the N- and/or C-terminus of the MIBD; and (c) a cleavable bond which attaches the sequence to the SP. The S-protecting group can be removed without cleaving the sequence from the SP;

(4) a combinatorial library targeted to **opioid receptors** of different sequence peptide members or peptidomimetic sequence synthesized in solution, where each library member comprises a peptide sequence or peptidomimetic sequence of 3 or more AARs (and/or mimics of these) bound to an SP. This sequence comprises (a) a sequence of 2 or more AARs (and/or mimics) which form a MIBD and which include at least one amino acid residue (and/or mimic) containing at least one S atom which is protected by an orthogonal S-protecting group; and (b) a sequence of one or more AARs (and/or mimics) at the N- and/or C-terminus of the MIBD; and

(5) metallopeptides, or their salts, of formula (I)-(VII), each complexed to a metal ion. R1-R2-R3-R4 (I), R5-R2-R6-R3-R7 (II), R5-R8-R2-R6-R3-R7 (III), R9-R1-R3-R10 (IV), R5-R11-R6-R12 (V), R5-R11-R13-R3-R10 (VI) or R14-R6-R15-R3-R16 (VII).

R1 = an L- or D-amino acid with a phenol moiety side chain and with an N atom available for complexation to a metal ion;

R2 = a neutral or basic L- or D-amino acid with an N atom available for complexation to a metal ion;

R3 = L- or D-Cys, L- or D-homoCys, L- or D-Pen, or a derivative or homologue of any of these, with both an N atoms and SH group available for complexation to a metal ion;

R4 = an L- or D-amino acid with a neutral aromatic side chain or a side chain with an aromatic ring substituted by halogen, nitro or and alkyl group; or a des-carboxyl derivative corresponding to such and L- or D-amino acid;

R5 = an L- or D-amino acid with a phenol moiety side chain, excluding des-carboxy derivatives;

R6 = an L- or D-amino acid with a neutral side chain or a side chain with an aromatic ring substituted by halogen, nitro or alkyl group, and with an N atom available for complexation to a metal ion;

R7 = a free carboxylate or terminal amide of R3 or a neutral or basic L- or D-amino acid, or a des-carboxyl derivative corresponding to such an L- or D-amino acid;

R8 = a neutral or basic L- or D-alpha or-omega amino acid, or a derivative of this;

R9 = an L- or D-amino acid with a basic functional group side chain, and with an N atom available for complexation to a metal ion;

R10 = a free carboxylate, primary amide or aryl or aralkyl chain substituted amide derivative of R3, or an L- or D-amino acid with a neutral aromatic side chain or side chain with a ring substituted by halogen, nitro or an alkyl group;

R11 = L- or D-Cys, L- or D-homoCys, L- or D-Pen, or a derivative or homologue of these, with an SH group available for complexation to a metal ion;

R12 = a neutral L- or D-amino acid with an N atom available for complexation to a metal ion, and with a terminal amide with an N atom available for complexation to a metal ion;

R13 = an L- or D-amino acid with a neutral aliphatic or aromatic side

chain or side chain with a ring substituted by halogen, nitro or an alkyl group, and which has an N atom available for complexation to a metal ion;

R14 = a neutral or basic L- or D-alpha or -omega amino acid, or a derivative of this, excluding higher omega-amino aliphatic carboxylic acid homologues;

R15 = a L- or D-amino acid with an N atom available for complexation to a metal ion and hydrogen bond forming groups in the side chain;

R16 = an L- or D-amino acid with a phenol moiety side chain, including des-carboxy derivatives.

ACTIVITY - Analgesic; immunomodulator; antiinflammatory; neuroleptic; tranquilizer; anorectic.

MECHANISM OF ACTION - **Opioid receptor agonist; opioid receptor** antagonist.

USE - The materials described above are **agonists**, antagonists or mixed **agonist**/antagonists of **opioid receptors**, including mu -, delta - and **kappa-opiate receptors**. They can be used in treatment of pain and may be used to treat various addictions (including morphine, alcohol or cocaine addiction). They may also be useful in treatment of autoimmune diseases, inflammation, **pruritus**, irritable bowel syndrome, psychotic disorders or gastrointestinal disorders. They may also be used to suppress appetite.

ADVANTAGE - The above peptides are substantially more specific for one or more **opioid receptors** when complexed with a metal than when not complexed with a metal ion. They are less susceptible to degradation by proteases and other enzymes than are conventional peptides, and are suitable for administration by means other than parenteral administration.

Dwg.0/0

FS CPI GMPI
FA AB; DCN
MC CPI: B04-C01; B05-A03; B14-C01; B14-C03; B14-E10; B14-E10C; B14-E12; B14-G02A; B14-G02D; B14-J01B3; B14-L01; B14-L06; B14-M01A; B14-M01C; B14-N17
TECH UPTX: 20010822

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The peptides may be prepared using known peptide synthesis methods. The orthogonal S-protecting group is, e.g., S-thio-butyl, acetamidomethyl, 4-methoxytrityl, S-sulfonate or 3-nitro-2-pyridinesulfenyl.

L108 ANSWER 3 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-244295 [25] WPIX
DNC C2001-073269
TI Agents for treating neuropathic pain comprise morphinan derivative.
DC B02
IN ENDO, T; KAWAMURA, K; KURAISHI, Y; NAGASE, H; SHIRAKI, K; SUZUKI, T; TANAKA, T
PA (TORA) TORAY IND INC
CYC 22
PI WO 2001014383 A1 20010301 (200125)* JA 33p C07D489-06
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA CN JP US
ADT WO 2001014383 A1 WO 2000-JP5690 20000824
PRAI JP 1999-236778 19990824
IC ICM C07D489-06
ICS A61K031-4738; A61K031-485; A61K045-00; A61P025-04; C07D471-04; C07D489-08
AB WO 200114383 A UPAB: 20010508

NOVELTY - Agents for treating neuropathic pain comprise a morphinan derivative (I).

DETAILED DESCRIPTION - Agents for treating neuropathic pain comprise a morphinan derivative of formula (I) or its acid addition salt.

R1 = Alk (optionally substituted by furan-2-yl or thiophen-2-yl), 4-7C cycloalkylalkyl, 5-7C cycloalkenylalkyl, 6-12C aryl, 7-13C aralkyl, 4-7C alkenyl or allyl;

Alk = 1-5C alkyl;

R2 = H, OH, NO2, OCOAlk, OAlk, Alk or NR9R10;
R9 = H or Alk;
R10 = H, Alk or COR11;
R11 = H, phenyl or Alk;
R3 = H, OH, OCOAlk, or OAlk;
A = XC(=Y), XC(=Y)Z, X or XSO2;
X, Y, Z = NR4, S or O;
R4 = H, Alk or 6-12C aryl;
a = single or double bond;
B' = bond or 1-14C alkylene (optionally containing 1-3 unsaturated bonds, optionally substituted by 1 or more OAlk, OCOAlk, OH, F, Cl, Br, I, amino, NO2, CF3 or phenoxy, and optionally with 1-3 CH2 groups replaced by CO);
R5 = H or J;
J = phenyl, naphthyl, fluorenyl, pyridyl, quinolinyl, isoquinolinyl, pyrrolyl, furanyl thiophenyl, indolyl, benzofuranyl, benzothiophenyl or Cyc all optionally substituted by 1 or more Alk, OAlk, OCOAlk, OH, F, Cl, Br, I, amino, NO2, CN, SCN, CF3, OCF3 or methylenedioxy;
Cyc = 3-8C cycloalkyl or 3-8C cycloalkenyl both with optionally with one CH2 replaced by NH, S or O;
R6, R7 = H, OH, OAlk or OCOAlk; or
R6+R7 = O, CH2 or S; and
R8 = H, Alk or COAlk.
N.B. b has not a definition.
INDEPENDENT CLAIMS are also included for:
(1) an animal model for neuropathic pain comprising administering (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octohydro-transquinolino(2,3-g)isoquinoline to the animal; and
(2) compounds for treating neuropathic pain obtained using the above model.
ACTIVITY - Analgesic. In a (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-transquinolino(2,3-g)isoquinoline induced neuropathic pain model in mice (-)-17-cyclopropyl-3,14 beta -dihydroxy-4,5 alpha -epoxy-6 beta -(N-methyl-trans-3-(3-furyl)acrylamido)morphinan hydrochloride at 0.056 mg/kg significantly reduced **scratching** biting and licking.
MECHANISM OF ACTION - **Kappa opioid receptor agonists**.
USE - (I) are useful as **kappa opioid receptor agonists** useful for treating neuropathic pain e.g. causalgia and pain due to diabetes, alcohol or other toxicities, amyloidosis, viral infections, trigeminal headaches, post-herpes zoster neuralgia, cerebral fibrosis, fevers, AIDS, multiple sclerosis and Alzheimer's disease.
Dwg.0/8
FS CPI
FA AB; GI; DCN
MC CPI: B04-A04; B14-C01

L108 ANSWER 4 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-234235 [24] WPIX
CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30]; 1999-508187 [42]; 2000-022101 [54]; 2000-194848 [17]; 2000-256918 [22]; 2000-328360 [27]; 2000-349606 [29]; 2001-440271 [38]
DNC C2001-070038
TI Prevention or treatment of **pruritus**, caused by e.g. anaphylactic reaction, enterobiasis or asteatotic eczema comprises administering a composition comprising N-(2-aminocyclohexyl)-N-methyl-phenylalkanoamide derivatives.
DC A23 A96 B03
IN CHANG, A; DEHAVEN-HUDKINS, D L; FARRAR, J J; GAUL, F; KRUSE, L I; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y
PA (ADOL-N) ADOLOR CORP
CYC 1
PI US 6180623 B1 20010130 (200124)* 71p A61K031-337
ADT US 6180623 B1 CIP of US 1996-612680 19960308, CIP of US 1997-796078

19970205, Div ex US 1997-891833 19970714, Div ex US 1998-45522 19980321, Div ex US 1999-307517 19990507, US 1999-436057 19991108
FDT US 6180623 B1 CIP of US 5646151, CIP of US 5688955, Div ex US 5763445, Div ex US 5981513, Div ex US 6028063
PRAI US 1997-891833 19970714; US 1996-612680 19960308; US 1997-796078 19970205; US 1998-45522 19980321; US 1999-307517 19990507; US 1999-436057 19991108
IC ICM A61K031-337
ICS A61K031-535; C07D273-08
AB US 6180623 B UPAB: 20010822
NOVELTY - Prevention or treatment of **pruritus** comprises administering a composition comprising a N-(2-aminocyclohexyl)-N-methyl-phenylalkanoamide derivative (I) or its salt.

DETAILED DESCRIPTION - Prevention or treatment of **pruritus** comprises administering a composition comprising a compound of formula (I) or a salt of (I), other than (plus or minus)-trans-3,4-dichloro-N-methyl-N-(2-dimethylaminocyclohexyl)-phenylacetamide hydrochloride and (plus or minus)-trans-3,4-dichloro-N-methyl-N-(2-pyrrolidinocyclohexyl)-phenylacetamide hydrochloride, in a vehicle.

n = 1-3;

R1, R2 = CH3, (CH2)m, CH2CH(OH)CH2CH2, CH2CH(F)CH2CH2, (CH2)2O(CH2)2 or (CH2)2CH=CHCH2;

m = 4-8;

R3, R4 = H, OCH3, alkyl, or -O(CH2)2;

X9 = (a) 1-4 of halo, CF3, OCH3, SO2NH(CH2)qCOOH, NH2, NHSO2CH3, NHP(O)(OBn)2, NHP(O)(OH)2, NH(CH2)qCOOH, SO2CH3, OP(O)(OBn)2, OP(O)(OH)2, COOH, O(CH2)qCOOH, O(CH2)qSO3H and O(CH2)qOPO3H2 or (b) a group of formula (i)-(iii):

q = 1-20;

t = 1-20;

R5 = H or CH3C(O)-; and

X6 = CO2H, NHSO2CH3, NHP(O)(OBn)2, NHP(O)(OH)2, OP(O)(OBn)2 or OP(O)(OH)2;

Provided that the compound of formula (I) is not (+ or -)-trans-3,4-dichloro-N-methyl-N-(2-(dimethylamino)cyclohexyl)-phenylacetamido hydrochloride or (+ or -)-trans-3,4-dichloro-N-methyl-N-(2-(1-pyrrolidinyl)cyclohexyl)-phenylacetamido hydrochloride or their salts.

ACTIVITY - Analgesic; anti-hyperalgesic; **antipruritic**; antithyroid.

Testing was performed in a **scratch** mouse model. 100 microliters of the vehicle 20% v/v cremaphor EL (3-5 doses) was injected subcutaneously into the backs of the necks of mice 20 minutes before challenging them with 100 microliters of Compound 48/80 (shown to produce an **itching** sensation in humans) (2 micrograms/ml, 50 micrograms) which was also injected subcutaneously into the backs of the necks of the mice. One minute later the mice were observed for 30 minutes and the number of hind leg **scratching** movements directed at the neck recorded. The vehicle-injected mice **scratched** 79 plus or minus 16 times in the 30 minutes after being challenged with Compound 48/80. Then, various doses of the compounds to be tested for **antipruritic** activity were administered subcutaneously to the backs of the necks of the mice. One minute after administration, the mice were again observed for 30 minutes and the number of hind leg **scratching** movements recorded as before. The means values for **scratching** were normalized to relative percentage antagonism of **scratching** and then plotted versus the dose of test compounds. Interval estimates of mean A50 were determined by non-linear regression analysis and the mean % inhibition of **scratching** calculated. The compounds tested showed dose-dependent activity in the range from 15-95% based upon subcutaneous doses of 0.5-10.0 mg/kg.

MECHANISM OF ACTION - (I) are **kappa opioid receptor agonists**.

USE - For preventing or treating **pruritus**, especially caused by anaphylactic reaction, urticaria, chiggers, secondary hyperparathyroidism, cutaneous larva migrans, dermal myiasis, onchocerciasis, pediculosis, enterobiasis, schistosome dermatitis or

asteatotic eczema.
ADVANTAGE - (I) are substantially devoid of CNS (central nervous system) effects.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: A12-V01; B07-D03; B10-B01B; B10-B02B; B14-B02; B14-G02; B14-G02A; B14-G02B; B14-L01; B14-N11; B14-N17
TECH UPTX: 20010502
TECHNOLOGY FOCUS - PHARMACEUTICALS - The composition comprises 0.1-50% w/w of (I).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared e.g. by:
(1) reaction of cyclohexene oxide with pyrrolidine to give the alcohol derivative of formula (II);
(2) conversion of (II) to a methane sulfonate derivative of formula (III);
(3) reaction of (III) with methylamine to give (plus or minus)-trans-2-pyrrolidinyl-N-methylcyclohexylamine of formula (IV);
(4) coupling of (IV) with various aryl acetic acids in the presence of N,N-dicyclohexylcarbodiimide and pyridine to produce the desired arylacetamides of formula (V); and
(5) addition of a 1M etherial hydrochloric acid to (V) to give the hydrochloride salts of (V).

L108 ANSWER 5 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2001-090169 [10] WPIX
CR 1998-332207 [29]; 1999-131835 [11]; 1999-152855 [13]; 2000-072070 [06]; 2000-316903 [25]
DNC C2001-026321
TI Anti-**pruritic** pharmaceutical formulations comprise **kappa agonist** compounds.
DC B02
IN CHANG, A; COWAN, A; FARRAR, J J; KUMAR, V; ZHANG, W Y
PA (APOL-N) APOLOR CORP
CYC 1
PI US 6156769 A 20001205 (200110)* 20p A61K031-445
ADT US 6156769 A Div ex US 1997-892599 19970714, Div ex US 1998-64695 19980422, Div ex US 1998-184393 19981102, Div ex US 1999-411111 19991004, US 2000-488420 20000120
FDT US 6156769 A Div ex US 5760023, Div ex US 5869521, Div ex US 6004694, Div ex US 6048860
PRAI US 1997-892599 19970714; US 1998-64695 19980422; US 1998-184393 19981102; US 1999-411111 19991004; US 2000-488420 20000120
IC ICM A61K031-445
AB US 6156769 A UPAB: 20010220
NOVELTY - **Pruritus** in a mammal is prevented or treated by administering tetracyclic derivatives (I) as **kappa agonists**.
DETAILED DESCRIPTION - **Pruritus** in a mammal is prevented or treated by administering tetracyclic derivatives of formula (I) or their salts as **kappa agonists**.
a = single or double bond;
R1 = 1-5C alkyl, 4-7C cycloalkyl, 5-7C cycloalkenylalkyl, 6-12C aryl, 7-13C aralkyl, 4-7C alkenyl, allyl, furan-2-yl(1-5C)alkyl or thiophen-2-yl(1-5C)alkyl;
R2 = H, OH, NO2, 1-5C alkanoyloxy, 1-5C alkoxy or NR9R10;
R9 = H or 1-5C alkyl;
R10 = H, 1-5C alkyl or -C(=O)R11;
R11 = H, phenyl or 1-5C alkyl;
R3 = H, OH, 1-5C alkanoyloxy or 1-5C alkyl;
A = -XC(=Y)-, -XC(=Y)Z-, -X-, -XSO2- or -OC(OR4)R4-;
X, Y, Z = NR4, S or O;
R4 = H, 1-5C alkyl or 6-12C aryl;
B' = valence bond, alkylene group having 1-14C and optionally substituted with 1-5C alkoxy, 1-5C alkanoyloxy, OH, F, Cl, Br, I, NH2,

NO2, CN, CF3 or phenoxy; 1 to 3 methylene groups may be replaced with CO, acyclic unsaturated hydrocarbon containing 1-3 double bonds and/or triple bonds and having 2-14C atoms which is optionally substituted with 1-5C alkoxy, 1-5C alkanoyloxy, OH, F, Cl, Br, I, NH2, NO2, CN, CF3 or phenoxy and 1-3 methylene groups may be replaced with carbonyl, 1-14C hydrocarbon containing 1-5 thioether, ether and/or amino bonds, and when the hetero atoms are not bonded directly to A, 1-3 methylene groups may be replaced with carbonyl groups;

R5 = H or organic group optionally substituted with 1-5C alkyl, 1-5C alkoxy, 1-5C alkanoyloxy, OH, F, Cl, Br, I, NH2, NO2, CN, isothicyanate, CF3 or methylenedioxy, phenyl, naphthyl, fluorenyl, pyridyl, quinolinyl, isoquinolinyl or a group of formula (i) to (iv);

Q = N, O or S;

T = CH, N, S or O;

i = 0-5;

m, n = greater than 0 and m + n = less than 5;

R6 = H;

R7 = H, OH, 1-5C alkoxy, 1-5C alkanoyloxy; or

R6 + R7 = -O-, -CH2- or -S-; R8 = H, 1-5C alkyl or 1-5C alkanoyl.

ACTIVITY - **Antipruritic**; analgesic. The **antipruritic** activity of the compounds were evaluated using mouse **scratch** model under blind conditions as specified. A specified compound showed a 72 % inhibition of **scratching** at a dose of 5 mg/kg sc.

MECHANISM OF ACTION - The compounds (I) are **kappa opioid agonists** and possess anti-**pruritic** and antihyperalgesic activity.

USE - The compounds are useful for preventing or treating **pruritus** in mammals.

ADVANTAGE - The compounds are devoid of central nervous system effects.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B04-A04; B14-N17
TECH UPTX: 20010220

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Preparation: The compounds are prepared as described in various US4145435, US4359476, US4855316, and US5114945.

L108 ANSWER 6 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-349606 [30] WPIX
CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30]; 1999-508187 [42]; 2000-022101 [54]; 2000-194848 [17]; 2000-256918 [22]; 2000-328360 [27]; 2001-234235 [13]; 2001-440271 [38]
DNC C2000-106280
TI Use of selected **opioid kappa receptor agonists** with no action on the central nervous system to prevent or treat **pruritis**.
DC B03 B05
IN CHANG, A; GAUL, F; GUO, D; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y
PA (ADOL-N) ADOLOR CORP
CYC 1
PI US 6057323 A 20000502 (200030)* 119p A61K031-495
ADT US 6057323 A Cont of US 1996-612680 19960308, Div ex US 1997-796078 19970205, Div ex US 1997-899086 19970723, CIP of US 1998-34661 19980303, CIP of US 1998-150369 19980909, US 1998-183011 19981030
FDT US 6057323 A Cont of US 5646151, Div ex US 5688955, Div ex US 5744458
PRAI US 1998-183011 19981030; US 1996-612680 19960308; US 1997-796078 19970205; US 1997-899086 19970723; US 1998-34661 19980303; US 1998-150369 19980909
IC ICM A61K031-495
ICS C07D241-04
AB US 6057323 A UPAB: 20010822

NOVELTY - The use of **opioid kappa receptor**

agonists (I) with no activity in the central nervous system to prevent or treat **pruritis** is new.

DETAILED DESCRIPTION - The prevention and treatment of **pruritis** with **Kappa agonists** of formula (I) and their salts is new.

n = 3;

R1,R2 = CH3; or

R1 + R2 = (CH2)m, CH2CH(OH)(CH2)2, CH2CH(F)(CH2)2, (CH2)2O(CH2)2 or (CH2)2CH=CHCH2;

m = 4-8;

Ar1 = phenyl optionally substituted with 1 - 2 groups independently selected from halogen, OC4 (sic), SO2CH3, CF3, amino, alkyl or 3,4-dichloro, benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl or 9-fluorene;

Z' = P(O)(OBn)2, P(O)(OH)2, (CH2)pC(O)NHOH, (CH2)pCOOH, SO2CH3, SO2NH2,CO(CH2)pCH(NH2)COOH, COCH(NH2)(CH2)pCOOH, CO2CH3, CONH2, (CH2)pO(CH2)pCOOH, (CH2)pO(CH2)pCONHOH, (CH2)pNHSO2CH3, (CH2)pNHC(S)NHCH(COOH)(CH2)pCOOH, (CH2)pSO3H, tetrazol-5-ylmethyl or a group of formula (i);

Bn = CH2-phenyl;

p = 0-20;

R3,R4 = H or acyl;

X2 = COOH, NHSO2CH3, NHP(O)(OBn)2, NHP(O)(OH)2, OP(O)(OBn)2 or OP(O)(OH)2;

X, Y = CH2NHSO2CH3, CH2NHP(O)(OBn)2, NHP(O)(OH)2, CH2OP(O)(OBn)2, CH2OP(O)(OH)2, (CH2)qO(CH2)qCOOH, (CH2)qO(CH2)qSO3H, (CH2)qO(CH2)qCHNHOH, CH2NHC(S)NHCH(COOH)(CH2)qCOOH or a group of formula (ii);

q, r = 1 - 20; and

X3 = COOH, NHSO2CH3, NHP(O)(OBn)2, NHP(O)(OH)2, OP(O)(OBn)2 or OP(O)(OH)2;

ACTIVITY - Analgesic; anti-**pruritic**.

MECHANISM OF ACTION - **Opioid kappa receptor agonist**.

(I) were tested against (3H)-diprenorphine binding to cloned human **kappa receptor**. Methyl 4-(2-glycyl-4-(trifluoromethylphenyl)acetyl)-3-(R,S)-((1-pyrrolidinyl)-methyl)-1-piperazinecarboxylate (Ia) had a Ki of 248 nM against (3H)-diprenorphine.

USE - Useful for preventing or treating **pruritis**.

ADVANTAGE - Unlike other treatments for **pruritis**, this therapy uses compounds with no activity within the central nervous system. Dependence and central nervous system side-effects are therefore avoided.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B05-B01J; B07-D11; B14-C01; B14-L01; B14-N17

L108 ANSWER 7 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-328360 [28] WPIX
CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30]; 1999-508187 [42]; 2000-022101 [54]; 2000-194848 [17]; 2000-256918 [22]; 2000-349606 [29]; 2001-234235 [13]; 2001-440271 [38]
DNC C2000-099459
TI New method for prevention or treatment of **pruritis** comprising administration of an arylacetamide compound which is a **kappa opioid agonist**..
DC B03
IN CHANG, A; GAUL, F; GUO, D; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y
PA (ADOL-N) ADOLOR CORP
CYC 1
PI US 6054445 A 20000425 (200028)* 121p A61K031-675
ADT US 6054445 A Cont of US 1996-612680 19960308, Div ex US 1997-796078 19970205, Div ex US 1997-899086 19970723, CIP of US 1998-34661 19980303, CIP of US 1998-150369 19980909, Div ex US 1998-183011 19981030, US 1999-307387 19990507
FDT US 6054445 A Cont of US 5646151, Div ex US 5688955, Div ex US 5744458, CIP

of US 5945443
PRAI US 1998-183011 19981030; US 1996-612680 19960308; US 1997-796078 19970205; US 1997-899086 19970723; US 1998-34661 19980303; US 1998-150369 19980909; US 1999-307387 19990507
IC ICM A61K031-675
ICS A61K031-40
AB US 6054445 A UPAB: 20010822
NOVELTY - A new method for prevention or treatment of **pruritis** comprises administration of an arylacetamide compound (I) or its salt.
DETAILED DESCRIPTION - A new method for prevention or treatment of **pruritis** comprises administration of an arylacetamide compound of formula (I) or its salt.
n = 1-3;
R1, R2 = CH3; or
R1+R2 = -(CH2)m-, -CH2CH(OR)(CH2)2-, CH2CH(F)(CH2)2-, -(CH2)2O(CH2)2- or -(CH2)2CHCH2-;
m = 4-8;
R = H, 1-12C alkyl, acyl or aroyl;
Ar' = phenyl (mono- or di-substituted with halogen, OCH3, OH, SO2CH3, CF3, NH2, 1-12C alkyl, CN, optionally substituted sulfamoyl, -NH(CH2)uCO2R', -NH(CH2)u(CH=CH)u(CH2)CO2R', -NHCO(CH2)u(CH=CH)u(CH2)uCO2R', -NHP(O)(O-benzyl)2, -NHP(O)(OR')2, -(CH2)uNHSO2CH3, -(CH2)uNHC(S)NHCH(CO2R')(CH2)uCO2R', -CONHOH or -(CH2)uCONHOH), (NHC(O)CH((CH2)vX8))v'NHR6 or -OCH2C(O)R7;
u = 0-5;
R' = H or 1-4C alkyl;
R6 = H or acetyl;
X8 = -CO2H, -NHSO2CH3, -NHP(O)(O-benzyl)2, -NHP(O)(OH)2, -OP(O)(OBn)2 or -OP(O)(OH)2;
R7 = -NH(CH2)vCO2H, -NH(CH2)vCH(NH2)(CO2H), -NHCH(CO2H)(CH2)vNH2, -NH(CH2)vSO3H, -NH(CH2)vPO3H2, -NH(CH2)vNHC(NH)NH2 or -NHCH(CO2H)CH2)vCO2H;
v = 1-20;
X4, X5 = H, halo, OH, OCH3, CF3, NO2, NH2 (optionally substituted with acyl, carbamate, 1-12C alkyl or aryl sulfonates) or COR''; and
R'' = OH, amide, 1-12C alkoxy, aryloxy or heteroaryloxy.
ACTIVITY - **Antipruritic.**
MECHANISM OF ACTION - **Kappa opioid agonist.**
In an in vitro binding assay, (Z)-(+/-)-trans-((7-amino-2-(3,4-dichlorophenyl)-N-methyl-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphth-1-yl)acetamido)4-oxo-butenoic acid had a Ki value of 28.0 nM for (3H)diprenorphine binding to the cloned human **kappa receptor.**
USE - (I) are useful for prevention or treatment of **pruritis** (claimed).
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B05-B01E; B05-B01F; B05-B01J; B05-B01K; B05-B01M; B05-B01N; B06-H; B07-H; B10-A08; B10-A09C; B10-A10; B10-A12C; B10-A13D; B10-A15; B10-A17; B10-A18; B10-B01; B10-B02B; B14-L01; B14-N17C

L108 ANSWER 8 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-316903 [27] WPIX
CR 1998-332207 [29]; 1999-131835 [11]; 1999-152855 [13]; 2000-072070 [06]; 2001-090169 [03]
DNC C2000-095770
TI Pharmaceutical treatment for **pruritis** in mammals involves administering compositions containing **kappa opioid receptor agonists.**
DC B03
IN CHANG, A; COWAN, A; FARRAR, J J; KUMAR, V; ZHANG, W Y
PA (ADOL-N) ADOLOR CORP
CYC 1
PI US 6048860 A 20000411 (200027)* 19p A61K031-495

ADT US 6048860 A Div ex US 1997-892599 19970714, Div ex US 1998-64695 19980422, Div ex US 1998-184393 19981102, US 1999-411111 19991004
FDT US 6048860 A Div ex US 5760023, Div ex US 5869521, Div ex US 6004964
PRAI US 1997-892599 19970714; US 1998-64695 19980422; US 1998-184393 19981102; US 1999-411111 19991004
IC ICM A61K031-495
ICS A61K031-445; A61K031-47; A61K031-50; A61K031-505
AB US 6048860 A UPAB: 20010220
NOVELTY - A method for treating **pruritis** in mammals by giving compositions comprising **kappa-opioid receptor agonists** (I) is new.

DETAILED DESCRIPTION - A new method for preventing and treating **pruritis** in mammals comprises the administration of a composition comprising **kappa-opioid receptor agonists** of formula (I) or its pharmaceutical salts.

R1,R2 = hydrogen (H), 3-6C alkenyl, 3-6C cycloalkyl or 4-12C cycloalkylalkyl; or

R1 + R2 = 2-8C polymethylene or 2-6C alkenylene either being optionally substituted with a heteroatom; or

NR1R2 = 5-membered ring (optionally containing an oxygen atom next to the nitrogen) or a 6-membered ring optionally containing 1 unsaturated unit optionally substituted with hydroxy, 1-6C acyloxy, oxo, methylene, COR10, OR11, NHR11 or N=NOR12;

R10,R12 = 1-6C alkyl;

R11 = H, 1-6C alkyl, aryl or aryl(1-6C alkyl); or

R3 = H, 1-6C alkyl or phenyl; or

R3 + R1 = -(CH2)3 or (CH2)4;

R4 = 1-6C alkyl or phenyl;

R5 = H; or

R4 + R5 = 2-5C linear polymethylene;

R6 = hydroxy, 1-6C alkyl, 1-6C hydroxyalkyl, 1-6C carboxyalkyl, phenyl, oxo, amino, carboxy, amido, optionally substituted methylene, COR13, COOR13, COCOOR13 or NRxCORx;

R13 = H or optionally substituted 1-10C hydrocarbon;

Rx = 1-6C alkyl;

R6 + E = 5-6 membered ring with one or more heteroatoms;

R7 = H; or

R7+R6 = single or fused 5-12C aryl or 5-12C heterocyclyl containing up to 4 heteroatoms from oxygen, sulfur and nitrogen optionally substituted with H, 1-6C alkyl, CH2OR14, halo, hydroxy, 1-6C alkoxy, 1-6C alkoxycarbonyl, thiol, 1-6C alkylthio, OCOR15, NHCOR16, NHSO2R17 or CH2SO2NR18R19;

R14, R15, R16, R17, R18, R19 = H, 1-6C alkyl, aryl or aralkyl;

A = (hetero)aryl optionally mono- or disubstituted with 1-6C alkyl, 2-6C alkenyl, 1-6C haloalkyl, 2-6C haloalkenyl, 2-6C haloalkynyl, aryl, aralkyl, hydroxy, 1-6C alkoxy, 1-6C haloalkoxy, thiol, 1-6C alkylthio, 1-6C haloalkylthio, halo, nitro, cyano, carboxy, aryloxy, aralkoxycarbonyl, carbamoyl, sulfonyl or sulfamoyl;

E = methylene, sulfur, oxygen or imino;

R8 = H or 1-6C alkyl;

R9 = H; or

R9 + R8 = (CRaRa)m-C(=Y)-;

Ra = H or 1-6C alkyl (up to 3 alkyls);

m = 1-3; and

Y = O or 2 hydrogens.

ACTIVITY - Anti-**pruritic**; anti-hyperalgesic.

Swiss albino mice were subcutaneously injected with Compound 48/80 (RTM) (2 mg/ml) following a subcutaneously injected pre-treatment of **kappa agonist** (10 mg/kg) in Cremaphor EL. Irritation, as measured by observing rear lib **scratching** movement, was reduced by 85 % compared to untreated controls.

MECHANISM OF ACTION - Kappa opioid receptor agonist.

USE - Useful for treating pruritis in mammals including that caused by irritation, inflammation, local infection, acute skin injury, toothache, poison ivy, allergy and dermatitis.

ADVANTAGE - The method is more effective than antihistamine and

opiate anti-pruritic therapies.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B14-C01; B14-C03; B14-G02A; B14-N17

L108 ANSWER 9 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-194848 [17] WPIX
CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30]; 1999-508187 [42]; 2000-022101 [54]; 2000-256918 [22]; 2000-328360 [27]; 2000-349606 [29]; 2001-234235 [13]; 2001-440271 [38]
DNC C2000-060334
TI Substituted heteroaromatic benzyl **kappa opioid agonists** are used in the prevention or treatment of pururitis.
DC B03
IN CHANG, A; DEHAVEN-HUDKINS, D L; FARRAR, J J; GAUL, F; KRUSE, L I; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y
PA (ADOL-N) ADOLOR CORP
CYC 1
PI US 6028063 A 20000222 (200017)* 67p A61K031-675
ADT US 6028063 A CIP of US 1996-612680 19960308, CIP of US 1997-796078 19970205, Div ex US 1997-891833 19970714, Div ex US 1998-45522 19980321, US 1999-307517 19990507
FDT US 6028063 A CIP of US 5646151, CIP of US 5688955, Div ex US 5763445
PRAI US 1997-891833 19970714; US 1996-612680 19960308; US 1997-796078 19970205; US 1998-45522 19980321; US 1999-307517 19990507
IC ICM A61K031-675
ICS A61K031-40
AB US 6028063 A UPAB: 20010822
NOVELTY - Prevention or treatment of pururitis comprises administration of substituted heteroaromatic benzyl derivatives (I)

DETAILED DESCRIPTION - Prevention or treatment of pururitis comprises administration of substituted heteroaromatic benzyl derivatives of formula (I).

n = 1-3;

R1 , R2 = CH3; or

R1+R2 = (CH2)m, CH2CH(OH)(CH2)2, CH2CH(F)(CH2)2, (CH2)2O(CH2)2 or (CH2)2CH=CH(CH2)2;

m = 4-8;

Ar = 3,4-dichlorophenyl, phenyl optionally mono- or di-substituted with T', benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl, or 9-fluorene;

T' = halogen, OCH3, SO2CH3, CF3, NH3 or alkyl;

X7 = NHSO2CH3, NHP(=O)(OBn)2, NHP(=O)(OH)2, (CH2)uNHSO2CH3, (CH2)uNHC(=S)NHCH(CO2)(CH2)uCO2H, CONHOH, (CH2)uCONHOH, OCH2C(=O)R7 or a group of formula (a);

Bn = benzoyl;

u = 1-5;

R6 = H or acetyl;

X8 = CO2H, NHSO2CH3, NHP(=O)(OBn)2, NHP(=O)(OH)2, OP(=O)(OBn)2 or OP(=O)(OH)2;

R7 = NH(CH2)vCO2H, NH(CH2)vCH(NH2)CO2H, NHCH(CO2H)(CH2)vNH2, NH(CH2)vSO3H, NH(CH2)vP(=O)(OH)2, NH(CH2)vNHC(NH)NH2 or NHCH(CO2H)(CH2)vCO2H;

V = (CH2)v; and

v = 1-20.

ACTIVITY - **Antipruritic**.

Testing for **antipruritic** activity was carried using the mouse **scratch** model, the **scratching** induced by compound 40/80 (RTM). 1 Mouse out of groups of 8-10 was subjected to standard challenge with the test compound and the number of hindleg **scratching** movements measured. Over a range of dosages the mean values of **scratching** for each group of mice were normalized relative to % antagonism of **scratching** and plotted against dosage. The compounds tested showed dose-dependant **antipruritic** activity of 15-95% based on dosages of 0.5-10 mg/kg.

No specific compound biological data given.
MECHANISM OF ACTION - **Kappa opioid agonist.**
USE - The compounds (I) are **kappa opioid agonists** used in the treatment of pururitis.
ADVANTAGE - **Kappa opioid agonists** are effective and have no central nervous system effects.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B07-D03; B07-D05; B07-D06; B14-C03; B14-N17

L108 ANSWER 10 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-072070 [06] WPIX
CR 1998-332207 [29]; 1999-131835 [11]; 1999-152855 [13]; 2000-316903 [25]; 2001-090169 [03]
DNC C2000-020499
TI Treatment and prevention of **pruritis** comprises administration of sulfonamide or acetamide derivatives.
DC B05 B06
IN CHANG, A; COWAN, A; FARRAR, J J; KUMAR, V; ZHANG, W Y
PA (ADOL-N) ADOLOR CORP
CYC 1
PI US 6004964 A 19991221 (200006)* 20p A61K031-495
ADT US 6004964 A Div ex US 1997-892599 19970714, Div ex US 1998-64695 19980422, US 1998-184393 19981102
FDT US 6004964 A Div ex US 5760023, Div ex US 5869521
PRAI US 1997-892599 19970714; US 1998-64695 19980422; US 1998-184393 19981102
IC ICM A61K031-495
AB US 6004964 A UPAB: 20010220
NOVELTY - Treatment and prevention of **pruritis** comprises administration of sulfonamide or acetamide derivatives (I), or their salts.
DETAILED DESCRIPTION - Treatment and prevention of **pruritis** comprises administration of sulfonamide or acetamide derivatives of formula (I), or their salts.
n = 0-1;
R = phenyl (optionally substituted by 1-3 Q1), alkylamino, dialkylamino, amido, sulfonamido, carboxamido (optionally mono- or disubstituted), ureido (optionally mono- or disubstituted), or 1-7C alkyl or 3-7C cycloalkyl (both optionally substituted by Q2), or B'R7, or DR8;
Q1 = halo, 1-6C alkyl, OH, OCONH2, OCONHalkyl, OCON(alkyl)2, 1-6C alkoxy, CF3, 1-4C alkoxy(1-4C)alkoxy, carboxy(1-4C)alkoxy, CN, NO2 or NH2;
Q2 = OH, NH2, amidino, guanidino, aminocarbonyl, carboxy, 1-6C alkoxy, 1-6C alkyloxycarbonyl, 3-6C alkenyloxycarbonyl, 3-6C alkynyloxycarbonyl, 1-6C alkanoyloxy, 1-6C alkylsulfide, 1-6C alkylsulfoxide, 1-6C alkylsulfone, 1-6C alkylaminocarbonyl, 1-6C acylamino, 1-6C acylmethylamino or 1-6C alkylamino;
B' = CH2, CH(CH3) or a single bond;
R7 = 6-10C aryl (optionally substituted by 1-3 Q1), alkylamino, dialkylamino, amido, sulfonamido, carboxamido (optionally mono- or disubstituted), ureido (optionally mono- or disubstituted);
D = a bond, CH2, CH(CH3), CH2O, CH(CH3)O, CH2S, CH(CH3)S, CH2NH or CH(CH3)NH;
R8 = a 4-6 membered heterocyclyl containing 1-4 heteroatoms selected from O, S or N (optionally S-substituted by oxygen, optionally N-substituted by oxygen, OH or 1-3C alkyl, or optionally C-substituted by one or more Q3);
Q3 = NH2, OH, SH, CN, halo, 1-3C alkoxy, 1-3 alkylamino, 1-3C acylamino, 1-3C acylmethylamino or 1-3C alkylthio;
R1, R2 = H, 1-6C alkyl, 3-5C alkenyl, 3-5C alkynyl, or 4-7C cycloalkyl; or
NR1R2 = 1-azetidinyl, 1-pyrrolidinyl (optionally 3-substituted by Q4), 1-piperazinyl (optionally 4-substituted by 1-3C alkyl), 1-morpholino, 2,5-dihydro-1H-pyrrolidin-1-yl, 3-azabicyclo(3.1.0)hexan-3-yl, or

3-azabicyclo(3.2.0)heptan-3-yl;
Q4 = OH, CH2OH, tri(1-6C)alkylsilyloxy, acyloxy, 1-6C alkyl, 1-6C alkoxy, or 1-6C alkanoyloxy;
R3 = H, 1-7C alkyl, or benzyl or heterocyclyl (optionally substituted by 1-3 Q5), or mono-, di- or trihalomethyl, CN, COR9, CH=NOR10, OR10, SR10, CH2CN, CH2OR10, CH2SR10, CH2S(O)R10, CH2S(O)2R10, CH2N(R10)(R11), CH2(R10)(R11) (sic), CH2N(R10)OH, CH2N(COR10)OH, CH2N(R10)COR11, CH2N(R10)S(O)2R11, or CH2OCOR10;
Q5 = halo, 1-4C alkyl, 1-4C alkoxy, or methoxycarbonyl;
R9 = H, OH, NH2, NHOH, NHOCH3, pyridylamino, NHN(CH3)2, 1-4C alkoxy, benzyloxy, 1-4C alkylamino, di(1-4C)alkylamino, 1-4C alkyl, or 1-4C alkylthio;
R10, R11 = H, 1-4C alkyl, 1-4C alkoxy, 7-11C phenylalkyl, or OR12;
R12 = H, 1-4C alkyl or a hydroxy protecting group;
X = CO or SO2;
Y = a bond (where only one of R4-R6 is attached), C, OC, SC, S(O)C, S(O)2C or CH2C;
R4-R6 = H, OH, alkoxy, 1-4C alkylenedioxy, 1-8C alkyl, 3-8C cycloalkyl; phenyl, naphthyl, biphenyl, indanyl, 1-tetralone-6-yl, furyl, thienyl, pyridyl, thiazolyl, benzofuryl, or benzothienyl (all optionally substituted by 1-3 Q6); or
R5+R6 = a group of formula (i);
Q6 = halo, CN, OCONH2, OCONHalkyl, OCON(alkyl)2, OCOalkyl, NHCHO, NHCOalkyl, ureido, NHCONHalkyl, N(alkyl)CONHalkyl, NHCON(alkyl)2, N(alkyl)CON(alkyl)2, NHSO2alkyl, COalkyl, CONH2, CONHalkyl, CON(alkyl)2, CH2CONH2, CH2CONHalkyl, CH2CON(alkyl)2, OCH2CONH2, OCH2CONHalkyl, OCH2CON(alkyl)2, 1-4C alkyl, 1-4C alkoxy, NH2, OH, NO2, CF3, SO2 alkyl, SOalkyl or mesyl;
R13, R14 = H, halo, OH, alkoxy, mono-, di- or trihalomethyl, NH2, NHalkyl, N(alkyl)2, NHCOalkyl, ureido, NO2 or methylenedioxy; and
D' = CH2, O, S, NH, CH2CH2, CH=CH, CH2NH or CH2N(alkyl).
ACTIVITY - **Antipruritic**; antihyperalgesic; antiinflammatory; dermatological; vulnerary.
Tests were performed in a mouse **scratch** model under blind conditions, using Swiss albino mice, to evaluate the **antipruritic** activity of (I). 3,4-Dichloro-N-methyl-N-(((1S)-1-(O-acetic acid-3-hydroxyphenyl)-2-(1-pyrrolidinyl)-ethyl)benzeneacetamide hydrochloride (Ia) gave 24, 72 and 85 % inhibition of **pruritis** at subcutaneous doses of 2.5, 5.0 and 10.0 mg/kg, respectively.
MECHANISM OF ACTION - **Kappa opioid agonists**.
USE - The method is used for the treatment and prevention of pruritis (claimed), such as that associated with irritation caused by inflammation following local infection, blisters, boils, or acute skin injuries (e.g. abrasions, superficial cuts or surgical incisions), toothaches, contusions, irritations, inflammatory skin conditions (e.g. poison ivy and allergic rashes), and dermatitis.
ADVANTAGE - The treatment is safe and effective.
Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B06-A01; B06-A03; B06-B01; B06-B02; B06-D13; B06-F05; B06-H; B07-A01; B07-B01; B07-D03; B07-D04C; B07-D11; B07-E03; B07-F01; B07-H; B08-D02; B08-D03; B10-A08; B10-A10; B10-A12C; B10-A17; B10-B01B; B14-C03; B14-N17

L108 ANSWER 11 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1998-347383 [30] WPIX
CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1999-508187 [42]; 2000-022101 [54]; 2000-194848 [17]; 2000-256918 [22]; 2000-328360 [27]; 2000-349606 [29]; 2001-234235 [13]; 2001-440271 [38]
DNC C1998-107342
TI Use of substituted piperazine derivatives which are **kappa opioid agonists** - for preventing or treating **pruritus**.
DC B02 B03

IN CHANG, A; DEHAVEN-HUDKINS, D L; FARRAR, J J; GAUL, F; KRUSE, L I; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y

PA (ADOL-N) ADOLOR CORP

CYC 75

PI US 5763445 A 19980609 (199830)* 67p A61K031-495
WO 9903468 A1 19990128 (199911) EN A61K031-40
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AU BA BB BG BR CA CN CU CZ EE GE GW HU ID IL IS JP KP KR LC LK LR LS LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA UZ VN YU
ZA 9806208 A 19990331 (199918) 142p A61K000-00
AU 9879801 A 19990210 (199925) A61K031-40
NO 9906352 A 20000313 (200023) A61K000-00
EP 998281 A1 20000510 (200027) EN A61K031-40
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
BR 9810712 A 20000905 (200048) A61K031-40
AU 725232 B 20001012 (200055) A61K031-40
JP 2001510154 W 20010731 (200148) 208p A61K031-495
KR 2001021853 A 20010315 (200159) A61K031-40
NZ 500439 A 20011026 (200176) A61K031-40

ADT US 5763445 A CIP of US 1996-612680 19960308, CIP of US 1997-796078 19970205, US 1997-891833 19970714; WO 9903468 A1 WO 1998-US12769 19980619; ZA 9806208 A ZA 1998-6208 19980713; AU 9879801 A AU 1998-79801 19980619; NO 9906352 A WO 1998-US12769 19980619, NO 1999-6352 19991220; EP 998281 A1 EP 1998-930400 19980619, WO 1998-US12769 19980619; BR 9810712 A BR 1998-10712 19980619, WO 1998-US12769 19980619; AU 725232 B AU 1998-79801 19980619; JP 2001510154 W WO 1998-US12769 19980619, JP 2000-502767 19980619; KR 2001021853 A KR 2000-700417 20000114; NZ 500439 A NZ 1998-500439 19980619, WO 1998-US12769 19980619

FDT US 5763445 A CIP of US 5646151, CIP of US 5688955; AU 9879801 A Based on WO 9903468; EP 998281 A1 Based on WO 9903468; BR 9810712 A Based on WO 9903468; AU 725232 B Previous Publ. AU 9879801, Based on WO 9903468; JP 2001510154 W Based on WO 9903468; NZ 500439 A Div in NZ 513889, Based on WO 9903468

PRAI US 1997-891833 19970714; US 1996-612680 19960308; US 1997-796078 19970205

IC ICM A61K000-00; A61K031-40; A61K031-495
ICS A61K031-404; A61K031-405; A61K031-4439; A61K031-496; A61P017-04; C07D401-12

ICA C07D207-12; C07D241-04; C07D295-12; C07D403-06; C07D403-12

AB US 5763445 A UPAB: 20011227
A method for prevention or treatment of **pruritus** comprises administration of a substituted piperazine derivative of formula (I) in a carrier: n = 1-3; R1, R2 = CH3, or together are -(CH2)m, -CH2CH(OH)(CH2)2-, CH2CH(F)(CH2)2-, -(CH2)2O(CH2)2- or -(CH2)2CH=CHCH2-; m = 4-8; Ar = Ph optionally substituted with 1 or 2 halo, OMe, SO2Me, CF3, NH2, alkyl or 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorenyl; Z = -P(O)(OBn)2, -P(O)(OH)2, -(CH2)pC(O)NHOH, -(CH2)pCO2H, -SO2Me, -SO2NH2, -CO(CH2)pCH(NH2)(CO2H), COCH(NH2)(CH2)pCO2H, -CO2Me, -CONH2, (CH2)pO(CH2)pCO2H, -(CH2)pO(CH2)pCONHOH, (CH2)pNHSO2Me, -(CH2)pNHC(S)NHCH(CO2H)(CH2)pCO2H, (CH2)pSO3H or a group of formula (i) or (ii): p = 0-20; R3 = H or Ac; X2, X3 = CO2H, -NHSO2Me, NHP(O)(OBn)2, NHP(O)(OH)2, OP(O)(OBn)2 or OP(O)(OH)2; X, Y = -CH2NHSO2Me, -CH2NHP(O)(OBn)2, -CH2NHP(O)(OH)2, CH2OP(O)(OBn)2, -CH2OP(O)(OH)2, -(CH2) qO(CH2)qCO2H, (CH2)qO(CH2)qSO3H, -(CH2)qO(CH2)qCHNHOH, CH2NHC(S)NHCH(CO2H)(CH2)qCO2H or a group of formula (iii): q, r = 1-20; R4 = H or Ac.
USE - (I) are **kappa opioid agonists**, useful as analgesics and for the treatment of **pruritus** (**itch**).
ADVANTAGE - (I) do not cause substantial central nervous system effects, and would not cause side effects associated with centrally acting **kappa opiate receptor agonists**.
Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B05-B01J; B05-B01M; B06-A01; B06-B01; B07-D03; B07-D05; B07-D11; B07-D13; B07-E03; B14-C01; B14-G02A; B14-N17

L108 ANSWER 12 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1998-322462 [28] WPIX
DNC C1998-099185
TI Anti-**pruritic** agent - comprises an **opioid kappa-receptor agonist**, especially new morphinane quaternary ammonium salts and N-oxide compounds.
DC B02 B03
IN ENDOH, T; KAMEI, J; KAWAMURA, K; NAGASE, H; TANAKA, T; UTSUMI, J
PA (TORA) TORAY IND INC; (TORA) TORAY KK
CYC 26
PI WO 9823290 A1 19980604 (199828)* JA 92p A61K045-00
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA CN JP KR NO NZ US
AU 9749683 A 19980622 (199844)
NO 9803431 A 19980924 (199848) A61K031-40
EP 897726 A1 19990224 (199912) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI NL PT SE
JP 10524506 X 19990608 (199933)
CN 1214634 A 19990421 (199934)
NZ 331001 A 20000526 (200033) A61K031-40
KR 99081978 A 19991115 (200052) A61K045-00
US 6174891 B1 20010116 (200106) A61K031-485
AU 738743 B 20010927 (200170) A61K045-00
US 6316461 B1 20011113 (200173) A61K031-485
ADT WO 9823290 A1 WO 1997-JP4267 19971121; AU 9749683 A AU 1997-49683 19971121; NO 9803431 A WO 1997-JP4267 19971121, NO 1998-3431 19980724; EP 897726 A1 EP 1997-912539 19971121, WO 1997-JP4267 19971121; JP 10524506 X WO 1997-JP4267 19971121, JP 1998-524506 19971121; CN 1214634 A CN 1997-193343 19971121; NZ 331001 A NZ 1997-331001 19971121, WO 1997-JP4267 19971121; KR 99081978 A WO 1997-JP4267 19971121, KR 1998-705696 19980724; US 6174891 B1 WO 1997-JP4267 19971121, US 1998-117052 19980824; AU 738743 B AU 1997-49683 19971121; US 6316461 B1 Div ex US 1998-117052 19980824, US 2000-615540 20000713
FDT AU 9749683 A Based on WO 9823290; EP 897726 A1 Based on WO 9823290; JP 10524506 X Based on WO 9823290; NZ 331001 A Based on WO 9823290; KR 99081978 A Based on WO 9823290; US 6174891 B1 Based on WO 9823290; AU 738743 B Previous Publ. AU 9749683, Based on WO 9823290; US 6316461 B1 Div ex US 6174891
PRAI JP 1996-313476 19961125
IC ICM A61K031-40; A61K031-485; A61K045-00
ICS A61K031-47; A61K031-54; C07D221-28; C07D279-12; C07D295-14; C07D489-00; C07D489-100; C07D491-08
AB WO 9823290 A UPAB: 19980715
Antipruritic agent comprises an **opioid kappa -receptor agonist**. Also claimed are morphinane quaternary ammonium salt derivatives and morphinane N-oxide derivatives of formula (I): Q = O- or R6X-; R1 = 1-5C alkyl, 4-7C cycloalkylalkyl, 5-7C cycloalkenylalkyl, 7-13C aralkyl, 4-7C alkenyl or aryl; R2 = H, OH, NO2, 1-5C alkanoyloxy, 1-5C alkoxy or 1-5C alkyl; R3 = H, OH, 1-5C alkanoyloxy or 1-5C alkoxy; R4 = H, 1-5C alkyl or 6-12C aryl; A = 1-6C alkylene, CH=CH or C triple bond C; R5 = phenyl, naphthyl, furyl, benzofuryl or a group of formula (i)-(iii): all optionally substituted by Q. N.B. no bonding group is shown for any of R5. T = CH or O; l = 1-5; m+n = at most 5; Q = 1-5C alkyl, 1-5C alkoxy, 1-5C alkenoyloxy, OH, F, Cl, Br, I, NO2, CN, isothiocyanato, CF3, CF3O or methylenedioxy; R5 and X are not defined in the claims in the disclosure; R6 = 1-5C alkyl or aryl; and X = anion.

(I) are prepared by reacting a compound corresponding to (I; Q is absent) with R6X, CH3SO3R6 or a peracid.

USE - The agent including compounds (I) are useful for the treatment and prevention of **pruritus** including **pruritus** accompanying atopic dermatitis, neurodermatitis, contact dermatitis, dermatitis due to mites, age related **skin** disorders, insect bites, photosensitivity, blisters athlete's foot, psoriasis, internal

conditions (such as malignant tumours, liver disorders, diabetes, and renal insufficiency) and pregnancy. Dosage is 0.1 mu g - 1000 mg/day orally or 0.001 ng/m2-10 mg/m2 topically.
Dwg.0/1
FS CPI
FA AB; GI; DCN
MC CPI: B04-A04; B14-A04; B14-H01; B14-N17B; B14-N17C; B14-S04

L108 ANSWER 13 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1997-340994 [31] WPIX
DNC C1997-109521
TI New **opioid** peptide(s) which bind mu **receptors** specifically - have **agonist** or antagonist activity and are used for study and localisation of mu **receptors** and to treat peripheral side effects of morphine etc..
DC B04 D16
IN DOOLEY, C T; HOUGHTEN, R A
PA (TORR-N) TORREY PINES INST MOLECULAR STUDIES
CYC 1
PI US 5641861 A 19970624 (199731)* 92p A61K038-08
ADT US 5641861 A US 1995-487006 19950607
PRAI US 1995-487006 19950607
IC ICM A61K038-08
ICS A61K038-04
AB US 5641861 A UPAB: 19970731
Peptides of formulae (1)-(7), (214), (221) and (222) are new:
Ac-Phe-Arg-Trp-Trp-Tyr-X-NH2 (1)
Ac-Arg-Trp-Ile-Gly-Trp-X-NH2 (2)
Trp-Trp-Pro-Lys-His-X-NH2 (3)
Trp-Trp-Pro-X1-NH2 (4)
Tyr-Pro-Phe-Gly-Phe-X-NH2 (5)
D-Ile-D-Met-D-Ser-D-Trp-D-Trp-(Gly)n-X2-NH2 (6)
D-Ile-D-Met-D-Thr-D-Trp-Gly-X2-NH2 (7)
Tyr-A1-B2-C3-NH2 (214)
Pm and red (MexHy-Tyr-(NMe)z-Tyr-(X3)z-NH2) (221)
Trp-Trp-Pro-D4-(His)z-(X)z-NH2 (222)
X = any natural amino acid; X1 = Lys or Arg; n and z = 0 or 1; X2 = Gly or the D form of any naturally occurring amino acid; A1 = D-norvaline or D-norleucine; B2 = Gly, Phe or Trp; C3 = Trp or naphthylalanine; x and y = 0-2, but not over 2 in total; X3 = Phe, DPhe or benzylamino; D4 = Lys or Arg; Pm and red indicate permethylation and reduction of all CO in peptide links to methylene.
USE - The new compounds are **opioids** specifically binding to the mu **receptor**. They are useful: (i) for in vitro assay and study of **opiate receptor** subtypes, particularly mu **receptors** in the brain; (ii) for in vivo localisation of **receptor** subtypes; and (iii) therapeutically to block the peripheral effects (e.g. constipation and **pruritus**) of centrally acting pain killers such as morphine.
ADVANTAGE - These compounds are very selective for the mu **receptor**, over binding to the delta and **kappa receptor** subtypes.
Dwg.0/7
FS CPI
FA AB; DCN
MC CPI: B04-C01A; B04-C01B; B04-N04A; B12-K04; B14-E09; B14-G02A; B14-L01; B14-L06; D05-H09

L108 ANSWER 14 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 1997-051893 [05] WPIX
DNC C1997-017171
TI **Opioid** peptide(s) selective for **kappa-opiate receptor** - useful as analgesics, to treat **receptor** -associated pathologies and to diagnose **receptor** subtype.
DC B04 D16
IN DOOLEY, C T; HOUGHTEN, R A

PA (TORR-N) TORREY PINES INST MOLECULAR STUDIES
CYC 22
PI WO 9640206 A1 19961219 (199705)* EN 28p A61K038-07
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9660429 A 19961230 (199716) A61K038-07
US 5610271 A 19970311 (199716) 18p A61K038-07
EP 833652 A1 19980408 (199818) EN A61K038-07
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
AU 699543 B 19981203 (199909) A61K038-07
JP 11512075 W 19991019 (200001) 19p C07K007-06
ADT WO 9640206 A1 WO 1996-US8871 19960603; AU 9660429 A AU 1996-60429 19960603; US 5610271 A US 1995-472219 19950607; EP 833652 A1 EP 1996-918080 19960603, WO 1996-US8871 19960603; AU 699543 B AU 1996-60429 19960603; JP 11512075 W WO 1996-US8871 19960603, JP 1997-501339 19960603
FDT AU 9660429 A Based on WO 9640206; EP 833652 A1 Based on WO 9640206; AU 699543 B Previous Publ. AU 9660429, Based on WO 9640206; JP 11512075 W Based on WO 9640206
PRAI US 1995-472219 19950607
REP 2.Jnl.Ref; US 4261883; US 5017689; US 5338668
IC ICM A61K038-07; C07K007-06
ICS A61K031-00; A61K038-00; A61K038-08; C07K005-10; C07K005-103; C07K005-107
AB WO 9640206 A UPAB: 19970129
Peptides of formulae Ac-A1-B2-C3-Arg-Tyr-Arg-Tyr-Arg-Arg-Arg-NH2 (I), (D)Phe-D4-E5-F6 (II) and (D)Nle-D4-E5-F6 (III) are new, in which A1 = Tyr or Arg, B2 = Arg or Phe, C3 = Thr, Phe or Met, D4 = (D)-naphthylalanine (NapAla) or (D)Phe, E5 = (D)Nle, Trp or (D)Ile, and F6 = (D)Arg or (D)-cyclohexylalanine (ChAla).
Peptides (I)-(III) are **opioid** peptides selective for the **Kappa** (K) **opiate receptor**. The peptides which act as K-**receptor agonists** are useful as analgesics, while those which act as antagonists are useful for treating pathologies associated with the K-**receptor**. For example, the peptides could be used to block unwanted peripheral effects of centrally acting pain killers (such as constipation and **pruritus** resulting from morphine admin.). Also, the novel peptides are useful in-vitro to study **opiate receptor** subtypes in brain and other tissues and similarly in-vivo to localise **opioid receptor** subtypes.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-C01A; B04-C01B; B14-C01; D05-H09
ABEQ US 5610271 A UPAB: 19970417
A peptide having the structure:
Ac-A1-B2-C3-Arg-Tyr-Arg-Tyr-Arg-Arg-Arg-NH2,
wherein A1 is Tyr or Arg;
B2 is Arg or Phe; and
C3 is Thr, Phe, or Met.
Dwg.0/0

=> d all abeq tech

L110 ANSWER 1 OF 1 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-022101 [02] WPIX
CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30]; 1999-508187 [42]; 2000-194848 [17]; 2000-256918 [22]; 2000-328360 [27]; 2000-349606 [29]; 2001-234235 [13]; 2001-440271 [38]
DNC C2000-005297
TI Prevention or treatment of **pruritus**.
DC B02 B03 D21
IN CHANG, A; DEHAVEN-HUDKINS, D L; FARRAR, J J; GAUL, F; KRUSE, L I; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y
PA (ADOL-N) ADOLOR CORP

CYC 1
PI US 5981513 A 19991109 (200002)* 73p A61K031-40
ADT US 5981513 A CIP of US 1996-612680 19960308, CIP of US 1997-796078 19970205, Div ex US 1997-891833 19970714, US 1998-45522 19980321
FDT US 5981513 A CIP of US 5646151, CIP of US 5688955, Div ex US 5763445
PRAI US 1997-891833 19970714; US 1996-612680 19960308; US 1997-796078 19970205; US 1998-45522 19980321
IC ICM A61K031-40
ICS C07D207-04
AB US 5981513 A UPAB: 20010822
NOVELTY - Prevention or treatment of **pruritus** comprises administering a tetrahydronaphthylacetamide derivative (I).
DETAILED DESCRIPTION - Prevention or treatment of **pruritus** comprises administering a tetrahydronaphthylacetamide derivative of formula (I) or its salt in a carrier.
n = 1-3;
R1, R2 = Me, (CH2)m, CH2CH(OH)CH22, CH2CH(F)(CH2)2, (CH2)2O(CH2)2 or (CH2)2CH=CH2 (sic);
Ar = phenyl (optionally substituted by 1 or 2 halo, OMe, SO2Me, CF3, amino, alkyl or 3,4-dichloro), benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl or 9-fluorenyl;
X4, X5 = OP(O)(OBn)2, OP(O)(OH), CO2H, SO3H, SO3H (sic), O(CH2)nCO2H, NHSO3Me, CONH(CH2)sCO2H, SO2NH(CH2)sCO2H, CONHCH((CHt)X6)(CONHCH((CH2)tX6)CO2H, (NHCOCH((CH2)nX6))NHR5 or SO2(NHCO(CH2)tX6)NHR5;
s = 1-5;
t = 1-20;
R5 = H or Ac;
X6 = CO2H, NHSO2Me, NHP(O)(OBn)2, NHP(O)(OH)2, OP(O)(OBn)2 or OP(O)(OH)2.
ACTIVITY - **Antipruritic**. In the late phase formalin test on Sprague Dawley rat paws 2-(7-((+/-)-trans-1-(N-3,4-dichlorophenylacetamido-N-methylamino)-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphthoxy))acetic acid (Ia) at 300 mu g showed 44% inhibition of flinching.
MECHANISM OF ACTION - **Opioid**-Antagonist-**Kappa**
USE - For preventing or treating **pruritus**.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B05-B01M; B05-B01N; B07-D03; B07-D05; B07-D06; B10-A08; B10-A09B; B10-B04B; B14-G02A; B14-N17; D08-B09A

=> d his

(FILE 'HOME' ENTERED AT 08:32:02 ON 18 JAN 2002)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:32:19 ON 18 JAN 2002
E KRUSE L/AU
L1 112 S E3,E5,E12-E14
E CHANG A/AU
L2 185 S E3,E5-E9
L3 22 S E118
E DEHAVEN/AU
L4 16 S E9-E11
L5 48 S E15-E18
E HUDKINS/AU
L6 1 S E4
E GAUL F/AU
L7 16 S E3-E5
E KUMAR V/AU
L8 772 S E3-E74
E KUMAR VIRENDRA/AU
L9 95 S E3
L10 7 S E2

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L11          1 S E5
                 E MARELLA M/AU
L12         24 S E3,E5,E6
                 E MAYCOCK A/AU
L13         64 S E3,E4,E6,E8,E9
                 E ZHANG W/AU
L14        554 S E3,E22
                 E ZHANG WEI/AU
L15       1248 S E3,E69
                 E ZHANG WEIYUAN/AU
L16         23 S E3
L17       3122 S L1-L16
                 E PRURIT/CW
L18        889 S E5,E6
                 E ANTIPRURIT/CW
                 E ITCH/CW
                 E PRURIGO/CW
                 E  HYPERALG/CW
L19        327 S E4
                 E PRURITIS/CT
                 E E4+ALL
L20        890 S E5,E4+NT
                 E HYPERALG/CT
                 E E4+ALL
L21       1152 S E1,E2
                 E PRURIT
L22       1629 S E5-E21
                 E PRURIG
L23         74 S E4-E8
                 E ITCH
L24       1292 S E3,E6,E9,E10,E15,E16,E17,E22
                 E SCRATCH
L25      16643 S E3,E5,E10,E13-24
L26          8 S E24,E26,E34
L27         29 S E38
L28          1 S E37
                 E ANTIITCH
L29         67 S E4
                 E ANTIPRUR
L30        274 S E5-E12
L31          2 S E93
L32          1 S E103
                 E ANTISCRATCH
L33        129 S E3,E4,E5
                 E ANTIHYPERALG
L34        110 S E4-E6
L35      20532 S L18-L34
L36       2743 S KAPPA(L)RECEPTOR(L)AGONIST(L)(OPIOID? OR OPIAT?)
L37       4877 S KAPPA(L)RECEPTOR(L)(OPIOID? OR OPIAT?)
L38         31 S L35 AND L36
L39         46 S L35 AND L37
L40        115 S (OPIOID? OR OPIAT?)(L)AGONIST AND L35
L41        235 S (OPIOID? OR OPIAT?)(L)RECEPTOR AND L35
L42         57 S (OPIOID? OR OPIAT?)(L)KAPPA AND L35
L43         57 S L38,L39,L42
L44        200 S L40,L41 NOT L43
L45         41 S KAPPA(L)AGONIST AND L35
L46         58 S L43,L45
L47        200 S L40,L41 NOT L46
L48          5 S L17 AND L46
L49          1 S L17 AND L47
L50          6 S L48,L49
                 E ADOLOR/PA,CS
L51         30 S E3-E14
L52         14 S L51 AND L35
L53          9 S L51 AND L36,L37
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L54          17 S L51 AND  (OPIOID? OR OPIAT?)(L)(AGONIST OR  RECEPTOR OR KAPPA
L55          13 S L51 AND KAPPA (L) AGONIST
L56           7 S L53,L54 AND L52
L57           7 S L50,L56
L58          17 S L52-L55 NOT L57
L59         251 S L46,L47 NOT L57,L58
L60         110 S L59 AND (PY<=1996 OR PRY<=1996 OR AY<=1996)
L61          18 S L60 AND (PERIPHERAL OPIATE RECEPTOR OR ANTIPRUR? OR SCRATCHIN
L62          42 S L57,L58,L61
L63          16 S L60 AND PRURITUS/CW,BI
L64          50 S L62,L63

     FILE 'HCAPLUS' ENTERED AT 09:08:46 ON 18 JAN 2002

     FILE 'EMBASE' ENTERED AT 09:09:18 ON 18 JAN 2002
                E PRURITIS/CT
L65       15299 S (PRURITUS+NT OR PRURIGO OR HYPERALGESIA)/CT
L66       19567 S PRURITIS OR PRURITUS OR PRURIGO OR ITCH OR ITCHING OR ITCHED
                E PRURIT
L67        1771 S E6-E24
L68       13458 S E25-E30,E33,E34
                E PRURIGO
L69         751 S E3-E5
                E ITCH
L70        3379 S E3,E7-E12
L71         407 S E14
                E SCRATCH
L72        2934 S E3,E7-E14,E16,E20-E23
                E HYPERALGES
                E HYPERALGAES
L73        3610 S E4-E12
L74          69 S E13-E24
                E ANTIPRURI
L75         298 S E1,E2,E4-E15
                E ANTIITCH
L76           3 S E3,E4
                E ANTISCRATCH
L77       23430 S L65-L76
L78         490 S KAPPA OPIATE RECEPTOR AGONIST+NT/CT
L79          17 S L77 AND L78
L80        1646 S L77 AND (OPIAT? OR OPIOID?)
L81         364 S L80 AND AGONIST
L82         774 S L80 AND RECEPTOR
L83         134 S L80 AND KAPPA
L84         430 S L81-L83 AND PY<=1996
L85           0 S L79 AND L84
L86         174 S L84 AND L81
L87         130 S L86 AND L82
L88          49 S L87 AND L83
L89           7 S L88 AND (?PRURIT? OR ?PRURIG? OR ?ITCH? OR ?SCRATCH?)
L90           1 S L89 AND FACIAL SCRATCHING

     FILE 'EMBASE' ENTERED AT 09:58:14 ON 18 JAN 2002

     FILE 'WPIX' ENTERED AT 09:58:23 ON 18 JAN 2002
                E PURUIT
                E PRURIT
L91         865 S E5-E16,E18,E19
                E PRURIG
L92          80 S E4-E9
                E ITCH
L93        1464 S E3-E6,E8-E13
                E SCRATCH
L94       15946 S E2-E5,E10-E24,E29,E30,E31,E32
                E ANTIPRUR
L95         527 S E4-E14
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                E ANTIITCH
L96           1 S E3
                E ANTISCRATCH
L97         161 S E3,E4
L98        1397 S SKIN(L)(TINGL? OR ITCH? OR PRURIT? OR PRURIGO? OR SCRATCH?)
L99       18521 S L91-L98
L100         50 S L99 AND (OPIOID? OR OPIAT?)
L101         18 S L100 AND KAPPA
L102         21 S L100 AND AGONIST
L103         35 S L100 AND RECEPTOR
L104         17 S L101 AND L102,L103
L105         18 S L102 AND L103
L106         24 S L104,L105
L107         17 S L106 AND L101
L108         14 S L102 AND L107

     FILE 'WPIX' ENTERED AT 10:06:16 ON 18 JAN 2002

     FILE 'WPIX' ENTERED AT 10:14:53 ON 18 JAN 2002
L109         10 S L106 NOT L108
L110          1 S L101 NOT L102-L109
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